EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	378	(544/234).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:44
L2	0	l1 and immunomodulat?	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:47
L3	4	l1 and (autoimmune adj disease)	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:48
L4	992	(514/247).CCLS. 248	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:48
L5	8	l1 and immunomodulat$	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:50
L6	38	l4 and immunomodulat$	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:51
L7	45	l4 and (autoimmune adj disease)	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:50
L8	7	l4 and immunomodulat$.clm.	US-PGPUB; USPAT; USOCR	OR	OFF	2007/01/19 12:51

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STN TRANSCRIPT
SN 10/547,448.

Connecting via Winsock to STN

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TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	OCT 23	The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded
NEWS 4	OCT 30	CHEMLIST enhanced with new search and display field
NEWS 5	NOV 03	JAPIO enhanced with IPC 8 features and functionality
NEWS 6	NOV 10	CA/CAplus F-Term thesaurus enhanced
NEWS 7	NOV 10	STN Express with Discover! free maintenance release Version 8.01c now available
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NEWS 9	NOV 20	CA/CAplus to MARPAT accession number crossover limit increased to 50,000
NEWS 10	DEC 01	CAS REGISTRY updated with new ambiguity codes
NEWS 11	DEC 11	CAS REGISTRY chemical nomenclature enhanced
NEWS 12	DEC 14	WPIDS/WPINDEX/WPIX manual codes updated
NEWS 13	DEC 14	GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS 14	DEC 18	CA/CAplus pre-1967 chemical substance index entries enhanced with preparation role
NEWS 15	DEC 18	CA/CAplus patent kind codes updated
NEWS 16	DEC 18	MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS 17	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS 18	DEC 27	CA/CAplus enhanced with more pre-1907 records
NEWS 19	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 20	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 21	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 22	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 18:10:32 ON 19 JAN 2007

=> file medline
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 18:10:39 ON 19 JAN 2007

FILE LAST UPDATED: 19 Jan 2007 (20070119/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s CD80/CD28
'CD28' IS NOT A VALID FIELD CODE
L1            0 CD80/CD28

=> s CD80
L2         4713 CD80

=> s l2 and IL2
           2028 IL2
L3           13 L2 AND IL2

=> s l2 and interleukin 2
         152547 INTERLEUKIN
           7836 INTERLEUKINS
         155262 INTERLEUKIN
                  (INTERLEUKIN OR INTERLEUKINS)
        3428681 2
          43948 INTERLEUKIN 2
                  (INTERLEUKIN(W)2)
L4          573 L2 AND INTERLEUKIN 2

=> s l2 and IL2 or interleukin 2 or interleukin II
           2028 IL2
         152547 INTERLEUKIN
           7836 INTERLEUKINS
         155262 INTERLEUKIN
                  (INTERLEUKIN OR INTERLEUKINS)
        3428681 2
          43948 INTERLEUKIN 2
                  (INTERLEUKIN(W)2)
         152547 INTERLEUKIN
           7836 INTERLEUKINS
```

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```
        155262 INTERLEUKIN
                 (INTERLEUKIN OR INTERLEUKINS)
        599709 II
           457 IIS
        599915 II
                 (II OR IIS)
            45 INTERLEUKIN II
                 (INTERLEUKIN(W)II)
L5       43972 L2 AND IL2 OR INTERLEUKIN 2 OR INTERLEUKIN II

=>  s l2 and (IL2 or interleukin 2 or interleukin II)
         2028 IL2
        152547 INTERLEUKIN
          7836 INTERLEUKINS
        155262 INTERLEUKIN
                 (INTERLEUKIN OR INTERLEUKINS)
       3428681 2
         43948 INTERLEUKIN 2
                 (INTERLEUKIN(W)2)
        152547 INTERLEUKIN
          7836 INTERLEUKINS
        155262 INTERLEUKIN
                 (INTERLEUKIN OR INTERLEUKINS)
        599709 II
           457 IIS
        599915 II
                 (II OR IIS)
            45 INTERLEUKIN II
                 (INTERLEUKIN(W)II)
L6         580 L2 AND (IL2 OR INTERLEUKIN 2 OR INTERLEUKIN II)

=> s l6 and (rheumatoid arthritis or multiple sclerosis or asthma or
transplantation or systemic lupus erythematosis or psoriasis)
         86205 RHEUMATOID
            17 RHEUMATOIDS
         86207 RHEUMATOID
                 (RHEUMATOID OR RHEUMATOIDS)
        118626 ARTHRITIS
             7 ARTHRITISES
        118627 ARTHRITIS
                 (ARTHRITIS OR ARTHRITISES)
         52227 RHEUMATOID ARTHRITIS
                 (RHEUMATOID(W)ARTHRITIS)
        500187 MULTIPLE
          4207 MULTIPLES
        502001 MULTIPLE
                 (MULTIPLE OR MULTIPLES)
         68862 SCLEROSIS
           113 SCLEROSES
         68904 SCLEROSIS
                 (SCLEROSIS OR SCLEROSES)
         34049 MULTIPLE SCLEROSIS
                 (MULTIPLE(W)SCLEROSIS)
         94534 ASTHMA
            87 ASTHMAS
         94537 ASTHMA
                 (ASTHMA OR ASTHMAS)
        386153 TRANSPLANTATION
          5961 TRANSPLANTATIONS
```

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50613257

```
         386712 TRANSPLANTATION
                  (TRANSPLANTATION OR TRANSPLANTATIONS)
         220400 SYSTEMIC
             10 SYSTEMICS
         220406 SYSTEMIC
                  (SYSTEMIC OR SYSTEMICS)
          50025 LUPUS
            380 ERYTHEMATOSIS
            289 SYSTEMIC LUPUS ERYTHEMATOSIS
                  (SYSTEMIC(W)LUPUS(W)ERYTHEMATOSIS)
          23243 PSORIASIS
L7           79 L6 AND (RHEUMATOID ARTHRITIS OR MULTIPLE SCLEROSIS OR ASTHMA OR
                TRANSPLANTATION OR SYSTEMIC LUPUS ERYTHEMATOSIS OR PSORIASIS)

=> s l7 and py<2004
      14563776 PY<2004
                  (PY<20040000)
L8           57 L7 AND PY<2004

=>

=> s l8 and review
         466267 REVIEW
          58423 REVIEWS
         511217 REVIEW
                  (REVIEW OR REVIEWS)
L9            0 L8 AND REVIEW

=> s l8 and (inhibit or inhibition)
         151474 INHIBIT
         103714 INHIBITS
         236250 INHIBIT
                  (INHIBIT OR INHIBITS)
         447386 INHIBITION
           3173 INHIBITIONS
         448778 INHIBITION
                  (INHIBITION OR INHIBITIONS)
L10          15 L8 AND (INHIBIT OR INHIBITION)

=> s l10 full
         151474 INHIBIT
         103714 INHIBITS
         236250 INHIBIT
                  (INHIBIT OR INHIBITS)
         447386 INHIBITION
           3173 INHIBITIONS
         448778 INHIBITION
                  (INHIBITION OR INHIBITIONS)
L11          15 L8 AND (INHIBIT OR INHIBITION)

=> d l11

L11  ANSWER 1 OF 15     MEDLINE on STN
AN   2003093351     MEDLINE
DN   PubMed ID: 12605124
TI   An engineered bifunctional recombinant molecule that regulates humoral and
     cellular effector functions of the immune system.
AU   Pizzolato Maryellen C; Fodor William L
CS   Alexion Pharmaceuticals, Inc., Cheshire, CT, USA.
```

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SO Transplantation, (2003 Feb 27) Vol. 75, No. 4, pp. 542-9.
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 27 Feb 2003
Last Updated on STN: 21 Mar 2003
Entered Medline: 20 Mar 2003

=> d l11 full
'FULL' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM,
ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):all

L11 ANSWER 1 OF 15 MEDLINE on STN
AN 2003093351 MEDLINE
DN PubMed ID: 12605124
TI An engineered bifunctional recombinant molecule that regulates humoral and cellular effector functions of the immune system.
AU Pizzolato Maryellen C; Fodor William L
CS Alexion Pharmaceuticals, Inc., Cheshire, CT, USA.

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50613257

SO Transplantation, (2003 Feb 27) Vol. 75, No. 4, pp. 542-9.
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 27 Feb 2003
Last Updated on STN: 21 Mar 2003
Entered Medline: 20 Mar 2003

AB BACKGROUND: Humoral and cellular defense mechanisms mediate the rejection of transplanted cells, tissues, and organs after allogeneic or xenogeneic transplantation. Inhibition of complement and T-cell costimulation are strategies aimed at increasing transplant survival. METHODS: Engineered novel fusion proteins that contain the functional domains of human CD152 (hCTLA4) or porcine CD152 (pCD152) and human CD59 (hCD152-hCD59, pCD152-hCD59) were developed to form bifunctional chimeric proteins that retain the effector functions of both moieties. Porcine aortic endothelial cells and murine Balb/3T3 cells were transduced or transfected to express the novel fusion proteins. RESULTS: Fluorescence-activated cell sorter analysis of hCD152-hCD59 transduced primary porcine aortic endothelial cells or hCD152-hCD59 and pCD152-hCD59 transfected Balb/3T3 cells determined that the molecules were expressed on the cell surface, and that they retained conformational epitopes. We demonstrate that hCD152-hCD59 and pCD152-hCD59 chimeric proteins inhibit complement-mediated cell lysis. In addition, hCD152-hCD59 or pCD152-hCD59 expression resulted in a significant reduction in T-cell activation as the result of CD152 engagement of porcine CD86 or murine CD80 in when Jurkat cells were cocultured with the hCD152-hCD59 or pCD152-hCD59 expressing cells. Antibody-blocking experiments or phosphatidylinositol phospholipase C removal of the glycosyl-phosphatidylinositol-linked molecules resulted in increased serum-mediated cytolysis and eliminated the costimulatory blockade. CONCLUSIONS: These data illustrate that a single molecule can confer resistance to humoral and cellular immune attack.

CT 3T3 Cells
Animals
*Antibody Formation: GE, genetics
Antibody Formation: IM, immunology
Antigens, CD: IM, immunology
Antigens, CD: ME, metabolism
Antigens, CD59: GE, genetics
*Antigens, CD59: IM, immunology
Antigens, CD59: ME, metabolism
Antigens, CD80: IM, immunology
Antigens, CD80: ME, metabolism
Antigens, CD86
Antigens, Differentiation: GE, genetics
*Antigens, Differentiation: IM, immunology
Antigens, Differentiation: ME, metabolism
Complement System Proteins: IM, immunology
Genetic Complementation Test
Humans
*Immunity, Cellular: GE, genetics
Immunity, Cellular: IM, immunology
*Immunoconjugates
Interleukin-2: IM, immunology
Jurkat Cells
Membrane Glycoproteins: IM, immunology

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50613257

Membrane Glycoproteins: ME, metabolism
Mice
Mice, Inbred BALB C
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: IM, immunology
Recombinant Proteins: GE, genetics
Recombinant Proteins: IM, immunology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Swine
T-Lymphocytes: IM, immunology
*Transplantation Immunology

RN 9007-36-7 (Complement System Proteins)

CN 0 (Antigens, CD); 0 (Antigens, CD59); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Antigens, Differentiation); 0 (CD86 protein, human); 0 (Cd86 protein, mouse); 0 (Immunoconjugates); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Recombinant Fusion Proteins); 0 (Recombinant Proteins); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

=> all 2-15
ALL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> all l11 2-15
ALL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l11 all 2-15

L11 ANSWER 2 OF 15 MEDLINE on STN
AN 2003036424 MEDLINE
DN PubMed ID: 12543104
TI Human CD34(+) blood cells induce T-cell unresponsiveness to specific alloantigens only under costimulatory blockade.
AU Arpinati Mario; Terragna Carolina; Chirumbolo Gabriella; Rizzi Simonetta; Urbini Benedetta; Re Francesca; Tura Sante; Baccarani Michele; Rondelli Damiano
CS Research Center for Transplant Immunology, Institute of Hematology and Medical Oncology Seragnoli, University of Bologna, Bologna, Italy.
SO Experimental hematology, (2003 Jan) Vol. 31, No. 1, pp. 31-8.
Journal code: 0402313. ISSN: 0301-472X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 25 Jan 2003
Last Updated on STN: 25 Feb 2003
Entered Medline: 24 Feb 2003
AB OBJECTIVES: The immunogenic role of human CD34(+) cells in allogeneic hematopoietic stem cell transplantation is controversial. In this study we tested the role of CD40 and CTLA4 ligands on CD34(+) cell costimulation of HLA-mismatched lymphocytes. MATERIALS AND METHODS: An

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anti-CD40L monoclonal antibody (hu5C8) and/or CTLA4-Ig molecule were used in primary mixed lymphocyte culture (MLC) with irradiated CD34(+) blood cells and allogeneic responders. Then, secondary MLC, cytotoxic activity, and effector cytokine expression and production were measured. RESULTS: Each reagent was able to reduce anti-CD34(+) cell alloreactivity, but only the combination of the anti-CD40L monoclonal antibody and CTLA4-Ig induced greater than 90% inhibition of T-cell response in primary MLC and prevented generation of cytotoxic T cells when priming with purified CD34(+) cells. Importantly, responder cells activated by allogeneic CD34(+) cells in the presence of anti-CD40L monoclonal antibody and CTLA4-Ig entered a state of antigen-specific unresponsiveness while responding to third party antigen, tetanus toxoid, or phytohemagglutinin, and showed suppression of interferon-gamma and increase of interleukin-10 expression and release. Interestingly, addition of interleukin-2 in secondary MLC did not reverse T-cell anergy. CONCLUSIONS: Thè results demonstrate that human CD34(+) blood progenitors stimulate T-cell responses potently and can induce T-cell unresponsiveness only when both B7:CD28 and CD40:CD40L pathways are blocked, with an increase of interleukin-10-producing cells. Therefore, our data allow design of in vivo studies aimed at achieving T-cell tolerance across HLA barriers by using purified CD34(+) cells and costimulatory blockade.

CT Adult
Antibodies, Monoclonal: IM, immunology
Antibodies, Monoclonal: PD, pharmacology
Antigen Presentation
*Antigens, CD28: IM, immunology
Antigens, CD34: AN, analysis
*Antigens, CD40: IM, immunology
*Antigens, CD80: IM, immunology
*Antigens, Differentiation: IM, immunology
*CD40 Ligand: IM, immunology
Cells, Cultured: IM, immunology
*Clonal Anergy: IM, immunology
HLA Antigens: IM, immunology
Hematopoietic Stem Cell Transplantation
*Hematopoietic Stem Cells: IM, immunology
Histocompatibility
Humans
Immunoconjugates: IM, immunology
Immunoconjugates: PD, pharmacology
Interleukin-10: BI, biosynthesis
*Isoantigens: IM, immunology
Lymphocyte Activation: DE, drug effects
*Lymphocyte Activation: IM, immunology
Lymphocyte Culture Test, Mixed
Research Support, Non-U.S. Gov't
*T-Lymphocytes, Cytotoxic: IM, immunology
Transplantation, Homologous: IM, immunology

RN 130068-27-8 (Interleukin-10); 147205-72-9 (CD40 Ligand)

CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD28); 0 (Antigens, CD34); 0 (Antigens, CD40); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (HLA Antigens); 0 (Immunoconjugates); 0 (Isoantigens); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L11 ANSWER 3 OF 15 MEDLINE on STN

AN 2002631269 MEDLINE

DN PubMed ID: 12389644

TI Experimental autoimmune encephalomyelitis in the Wistar rat: dependence of MBP-specific T cell responsiveness on B7 costimulation.

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AU Zhou Jing; Zhang Jia-Sheng; Ma Bao-Li; Mamula Mark J
CS Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520, USA.
SO Autoimmunity, (2002 May) Vol. 35, No. 3, pp. 191-9.
Journal code: 8900070. ISSN: 0891-6934.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200212
ED Entered STN: 23 Oct 2002
Last Updated on STN: 20 Dec 2002
Entered Medline: 19 Dec 2002
AB Experimental autoimmune encephalomyelitis (EAE) is an animal model of human multiple sclerosis that requires the activation of autoreactive T cells for the expression of pathology. EAE has been most frequently studied in the Lewis rat model as well as in several murine models of EAE including the PLJ and B10PL strains. In the present study we describe a novel model of EAE induced in the Wistar rat strain by immunization with guinea pig spinal cord antigens and pertussis toxin (PT). T cell responses were induced to myelin basic protein. Autoreactive T cells could be totally blocked by the in vitro treatment with CTLA4Ig, a protein that blocks the costimulation of autoreactive T cells. The addition of IL-2 could reverse the inhibition seen in vitro with CTLA4Ig. The effects of inhibition of B7 costimulation were also examined by an analysis of cytokine responses and IL-2 receptor on T cells. CTLA4Ig treatment in vitro reduced the expression of IL-2 receptor on T cells, enhanced T cell apoptosis and decreased the synthesis of IL-2, IFN-gamma and TNF-alpha. CTLA4Ig treatment had no effect on IL-10 synthesis by T cells, a cytokine implicated in the functions of regulatory T cell subsets. Overall, our studies support the rationale of B7 blocking therapies as a potential treatment for models of multiple sclerosis. The induction of EAE in the Wistar rat provides yet another novel model in which to examine the regulation of T cell autoimmunity.
CT Animals
*Antigens, CD80: PH, physiology
Antigens, Differentiation: PD, pharmacology
Apoptosis
Autoantibodies: BL, blood
Brain: PA, pathology
Cytokines: BI, biosynthesis
*Encephalomyelitis, Autoimmune, Experimental: ET, etiology
Encephalomyelitis, Autoimmune, Experimental: IM, immunology
Encephalomyelitis, Autoimmune, Experimental: PA, pathology
Enzyme-Linked Immunosorbent Assay
*Immunoconjugates
Lymphocyte Activation
*Myelin Basic Proteins: IM, immunology
Rats
Rats, Wistar
Receptors, Interleukin-2
*T-Lymphocytes: IM, immunology
CN 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (Autoantibodies); 0 (Cytokines); 0 (Immunoconjugates); 0 (Myelin Basic Proteins); 0 (Receptors, Interleukin-2); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L11 ANSWER 4 OF 15 MEDLINE on STN

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50613257

AN 2002116543 MEDLINE
DN PubMed ID: 11830501
TI Blockade of B7/CD28 in mixed lymphocyte reaction cultures results in the generation of alternatively activated macrophages, which suppress T-cell responses.
AU Tzachanis Dimitrios; Berezovskaya Alla; Nadler Lee M; Boussiotis Vassiliki A
CS Department of Adult Oncology, Dana Farber Cancer Institute, and the Division of Medical Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
NC AI 41584 (NIAID)
AI 43552 (NIAID)
HL 54785 (NHLBI)
SO Blood, (2002 Feb 15) Vol. 99, No. 4, pp. 1465-73.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200204
ED Entered STN: 20 Feb 2002
Last Updated on STN: 26 Apr 2002
Entered Medline: 25 Apr 2002
AB Blockade of B7/CD28 costimulation allows human haploidentical bone marrow transplantation without graft-versus-host disease. This study shows that blockade of B7/CD28 in anergizing mixed lymphocyte reaction (MLR) cultures of peripheral blood mononuclear cells results in the generation of alternatively activated macrophages (AAMphi). In contrast, priming MLR cultures result in generation of classically activated macrophages (CAMphi). AAMphi had enhanced expression of CD14, major histocompatibility complex class II, and CD23; produced alternative macrophage activation-associated CC-chemokine 1 (AMAC-1) chemokine; and displayed increased phagocytotic activity but decreased ability for antigen presentation. Suppression subtractive hybridization revealed that although AAMphi had undergone terminal maturation and differentiation, they entered a distinct gene expression program as compared with CAMphi and selectively expressed beta2-microglobulin, lysozyme, ferritin heavy and light chain, and the scavenger receptors macrophage mannose receptor and sortilin. Anergic T cells isolated from cultures that led to the development of AAMphi produced low amounts of interleukin-2 (IL-2), IL-4, and interferon-gamma, but high amounts of IL-10. Addition of anti-IL-10 neutralizing monoclonal antibody in anergizing cultures reversed the functional characteristics of AAMphi, indicating that at least one mechanism involved in the generation of AAMphi was mediated by IL-10. Importantly, when added in MLR cultures, AAMphi suppressed T-cell responses. Therefore, besides direct inhibition of T-cell costimulation, blockade of B7/CD28 may facilitate induction of T-cell unresponsiveness by generating AAMphi. Because in healthy individuals, AAMphi are found in the placenta and lung, where they protect from unwanted immune reactivity, the results suggest that AAMphi may play a critical role in the induction of transplantation tolerance.
CT Antibodies, Monoclonal: PD, pharmacology
Antigens, CD14: ME, metabolism
Antigens, CD28: DE, drug effects
*Antigens, CD28: IM, immunology
Antigens, CD80: DE, drug effects
*Antigens, CD80: IM, immunology
Cytokines: DE, drug effects
Cytokines: ME, metabolism

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50613257

Cytokines: PD, pharmacology
Histocompatibility Antigens Class II: ME, metabolism
Humans
Immunosuppression
Lymphocyte Activation: IM, immunology
Lymphocyte Culture Test, Mixed
Macrophage Activation: DE, drug effects
*Macrophage Activation: IM, immunology
Macrophages: DE, drug effects
Macrophages: IM, immunology
Macrophages: ME, metabolism
Phagocytosis: IM, immunology
Research Support, U.S. Gov't, P.H.S.
T-Lymphocytes: IM, immunology
CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD14); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Cytokines); 0 (Histocompatibility Antigens Class II)

L11 ANSWER 5 OF 15 MEDLINE on STN
AN 2001636270 MEDLINE
DN PubMed ID: 11688963
TI Local cytokine treatment of HPV16-associated tumours results in inhibition of their lung metastases.
AU Mikyskova R; Bubenik J; Mendoza L; Vonka V; Smahel M; Simova J; Jandlova T
CS Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague.
SO Clinical & experimental metastasis, (2000) Vol. 18, No. 7, pp. 581-7.
Journal code: 8409970. ISSN: 0262-0898.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 5 Nov 2001
Last Updated on STN: 23 Jan 2002
Entered Medline: 4 Dec 2001
AB Experiments were designed to examine whether local cytokine therapy of subcutaneous (s.c.) tumours results in inhibition of their lung metastases. Moderately immunogenic, major histocompatibility complex (MHC) class I and II negative. B7 negative, metastasizing murine carcinoma MK16 transplantable in syngeneic mice was obtained by co-transfection of human papilloma virus type 16 (HPV 16) E6/E7 and activated H-ras oncogene plasmid DNA into C57BL/6 kidney cells. After s.c. transplantation of the malignantly converted MK16 cells, the majority of the transplanted mice developed lung metastases; the number and size of the lung metastases increased with the increasing size of the s.c. tumour. Therapy of 5-day MK16 tumours by peritumoral administration of recombinant interleukin-2 (IL-2) and recombinant interleukin-12 (IL-12) inhibited growth of the s.c. MK16 tumour transplants and reduced the number of MK16 lung metastases. To investigate the antimetastatic effect of IL-2 and IL- 12 in a clinically more relevant setting, surgical minimal residual tumour disease was utilized. Subcutaneously growing MK16 carcinomas, 8-12 mm in diameter, were removed on day 30 and the operated mice were injected with IL-2 or IL- 12 on days 35-39 and 42-46 at the site of the operation. Treatment with IL-2 significantly reduced the percentage of MK16 tumour recurrences as well as the number of lung metastases, whereas the effect of IL- 12 was substantially weaker and statistically insignificant.

Erich Leeser

50613257

CT Check Tags: Female
Animals
Antigens, CD: ME, metabolism
Antigens, CD80: ME, metabolism
Antigens, CD86
*Antineoplastic Agents: TU, therapeutic use
*Carcinoma: DT, drug therapy
Carcinoma: SC, secondary
Carcinoma: VI, virology
Cell Division: DE, drug effects
Cell Line, Transformed
Histocompatibility Antigens: ME, metabolism
*Interleukin-12: TU, therapeutic use
*Interleukin-2: TU, therapeutic use
*Lung Neoplasms: DT, drug therapy
Lung Neoplasms: SC, secondary
Membrane Glycoproteins: ME, metabolism
Mice
Mice, Inbred C57BL
Neoplasm Transplantation
*Papillomavirus Infections: DT, drug therapy
Papillomavirus Infections: PA, pathology
Research Support, Non-U.S. Gov't
*Tumor Virus Infections: DT, drug therapy
Tumor Virus Infections: PA, pathology
RN 187348-17-0 (Interleukin-12)
CN 0 (Antigens, CD); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Antineoplastic Agents); 0 (Cd86 protein, mouse); 0 (Histocompatibility Antigens); 0 (Interleukin-2); 0 (Membrane Glycoproteins)

L11 ANSWER 6 OF 15 MEDLINE on STN
AN 2001333523 MEDLINE
DN PubMed ID: 11390449
TI Aspirin inhibits in vitro maturation and in vivo immunostimulatory function of murine myeloid dendritic cells.
AU Hackstein H; Morelli A E; Larregina A T; Ganster R W; Papworth G D; Logar A J; Watkins S C; Falo L D; Thomson A W
CS Thomas E. Starzl Transplantation Institute and Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA.
NC P01CA7343 (NCI)
R01AI 41011 (NIAID)
R01DK 49745 (NIDDK)
SO Journal of immunology (Baltimore, Md. : 1950), (2001 Jun 15) Vol. 166, No. 12, pp. 7053-62.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200108
ED Entered STN: 27 Aug 2001
Last Updated on STN: 27 Aug 2001
Entered Medline: 23 Aug 2001
AB Aspirin is the most commonly used analgesic and antiinflammatory agent. In this study, at physiological concentrations, it profoundly inhibited CD40, CD80, CD86, and MHC class II expression on murine, GM-CSF + IL-4 stimulated, bone marrow-derived myeloid dendritic cells (DC). CD11c and MHC class I expression were unaffected. The inhibitory action

was dose dependent and was evident at concentrations higher than those necessary to inhibit PG synthesis. Experiments with indomethacin revealed that the effects of aspirin on DC maturation were cyclooxygenase independent. Nuclear extracts of purified, aspirin-treated DC revealed a decreased NF-kappaB DNA-binding activity, whereas Ab supershift analysis indicated that aspirin targeted primarily NF-kappaB p50. Unexpectedly, aspirin promoted the generation of CD11c+ DC, due to apparent suppression of granulocyte development. The morphological and ultrastructural appearance of aspirin-treated cells was consistent with immaturity. Aspirin-treated DC were highly efficient at Ag capture, via both mannose receptor-mediated endocytosis and macropinocytosis. By contrast, they were poor stimulators of naive allogeneic T cell proliferation and induced lower levels of IL-2 in responding T cells. They also exhibited impaired IL-12 expression and did not produce IL-10 after LPS stimulation. Assessment of the in vivo function of aspirin-treated DC, pulsed with the hapten trinitrobenzenesulfonic acid, revealed an inability to induce normal cell-mediated contact hypersensitivity, despite the ability of the cells to migrate to T cell areas of draining lymphoid tissue. These data provide new insight into the immunopharmacology of aspirin and suggest a novel approach to the manipulation of DC for therapeutic application.

CT Check Tags: Male
Animals
*Aspirin: PD, pharmacology
Bone Marrow Cells: CY, cytology
Bone Marrow Cells: EN, enzymology
Bone Marrow Cells: IM, immunology
Bone Marrow Transplantation
Cell Differentiation: DE, drug effects
Cell Differentiation: IM, immunology
Cell Movement: DE, drug effects
Cell Movement: IM, immunology
Cell Survival: DE, drug effects
Cell Survival: IM, immunology
Cells, Cultured
DNA-Binding Proteins: AI, antagonists & inhibitors
DNA-Binding Proteins: ME, metabolism
Dendritic Cells: DE, drug effects
Dendritic Cells: EN, enzymology
*Dendritic Cells: IM, immunology
Dendritic Cells: TR, transplantation
Dermatitis, Contact: IM, immunology
Dose-Response Relationship, Drug
Endocytosis: DE, drug effects
Endocytosis: IM, immunology
*Growth Inhibitors: PD, pharmacology
Immunity, Cellular: DE, drug effects
Immunophenotyping
*Immunosuppressive Agents: PD, pharmacology
Injections, Subcutaneous
Integrin alphaXbeta2: BI, biosynthesis
Interleukin-10: AI, antagonists & inhibitors
Interleukin-10: SE, secretion
Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: BI, biosynthesis
Interleukin-2: AI, antagonists & inhibitors
Interleukin-2: BI, biosynthesis
*Lymphocyte Activation: DE, drug effects
Lymphocyte Culture Test, Mixed

Erich Leeser

Lymphoid Tissue: IM, immunology
Lymphoid Tissue: PA, pathology
Macrophages: CY, cytology
Macrophages: DE, drug effects
Macrophages: IM, immunology
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Myeloid Cells: DE, drug effects
Myeloid Cells: EN, enzymology
*Myeloid Cells: IM, immunology
Myeloid Cells: TR, transplantation
NF-kappa B: AI, antagonists & inhibitors
NF-kappa B: ME, metabolism
NF-kappa B p50 Subunit
Prostaglandin-Endoperoxide Synthases: PH, physiology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Signal Transduction: DE, drug effects
Signal Transduction: IM, immunology
T-Lymphocytes: DE, drug effects
T-Lymphocytes: IM, immunology
T-Lymphocytes: ME, metabolism

RN 130068-27-8 (Interleukin-10); 187348-17-0 (Interleukin-12); 50-78-2 (Aspirin)

CN 0 (DNA-Binding Proteins); 0 (Growth Inhibitors); 0 (Immunosuppressive Agents); 0 (Integrin alphaXbeta2); 0 (Interleukin-2); 0 (NF-kappa B); 0 (NF-kappa B p50 Subunit); EC 1.14.99.1 (Prostaglandin-Endoperoxide Synthases)

L11 ANSWER 7 OF 15 MEDLINE on STN

AN 2000409968 MEDLINE

DN PubMed ID: 10918497

TI Feasibility of CTLA4Ig gene delivery and expression in vivo using retrovirally transduced myeloid dendritic cells that induce alloantigen-specific T cell anergy in vitro.

AU Takayama T; Morelli A E; Robbins P D; Tahara H; Thomson A W

CS Thomas E Starzl Transplantation Institute, University of Pittsburgh Medical Center, PA 15213, USA.

NC AI 41011 (NIAID)
DK 49745 (NIDDK)

SO Gene therapy, (2000 Aug) Vol. 7, No. 15, pp. 1265-73.
Journal code: 9421525. ISSN: 0969-7128.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200008

ED Entered STN: 7 Sep 2000
Last Updated on STN: 7 Sep 2000
Entered Medline: 28 Aug 2000

AB Dendritic cells (DC) are highly specialised, bone marrow (BM)-derived antigen-presenting cells (APC) that initiate and regulate immune responses. They provide costimulatory signals (in particular, CD40 and the CD28 ligands CD80 and CD86) necessary for naive T cell activation. Functional expression of CD80 and CD86 is blocked by the fusion protein cytotoxic T lymphocyte antigen 4-immunoglobulin (CTLA4Ig), that promotes tolerance induction in animals. Here, replicating mouse (B10; H2b) myeloid DC progenitors, were retrovirally

transduced to express CTLA4Ig using the centrifugal enhancement method. Gene product was detected by immunocyto- or histochemistry. Maximal DC transduction efficiency was 62%. Compared with control, zeomycin-resistance gene (Zeo)-transduced DC, CTLA4Ig-expressing cells showed markedly impaired capacity to stimulate naive allogeneic (C3H; H2k) T cell proliferation and cytotoxic T lymphocyte (CTL) generation. Their ability to induce alloantigen-specific T cell hyporesponsiveness was reversed by exogenous IL-2 in secondary mixed leukocyte reactions (MLR). Following local (s.c.) transfer to allogeneic recipients, the genetically modified DC trafficked to T cell areas of draining lymphoid tissue, where transgene expression was detected. Ex vivo analysis of proliferative and CTL responses revealed donor-specific inhibition of alloimmune reactivity by the CTLA4Ig-transduced DC. This effect was associated with marked inhibition of interferon (IFN)-gamma production, but significant augmentation of IL-4 and IL-10 secretion. Thus, retroviral transduction of DC permits in vivo delivery of CTLA4Ig to the precise microenvironment where antigen (Ag) presentation occurs. Comparatively nonimmunogenic retroviral vectors, that allow permanent transgene expression in DC, and promote localized delivery of the immunosuppressive transgene product, promote immune deviation and Ag-specific T cell hyporesponsiveness.

CT Analysis of Variance
Animals
Antigens, Differentiation: AN, analysis
*Antigens, Differentiation: GE, genetics
Clonal Anergy
*Dendritic Cells: TR, transplantation
Gene Expression
*Gene Therapy: MT, methods
Genetic Vectors: AD, administration & dosage
*Immunoconjugates
Immunohistochemistry
*Immunosuppressive Agents
Interferon Type II: BI, biosynthesis
Interleukin-10: SE, secretion
Interleukin-2: PD, pharmacology
Interleukin-4: SE, secretion
Mice
Research Support, U.S. Gov't, P.H.S.
Retroviridae: GE, genetics
*T-Lymphocytes: IM, immunology
*Transfection: MT, methods
Transplantation, Homologous

RN 130068-27-8 (Interleukin-10); 207137-56-2 (Interleukin-4); 82115-62-6 (Interferon Type II)

CN 0 (Antigens, Differentiation); 0 (Immunoconjugates); 0 (Immunosuppressive Agents); 0 (Interleukin-2); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L11 ANSWER 8 OF 15 MEDLINE on STN
AN 1999443397 MEDLINE
DN PubMed ID: 10515374
TI Increased apoptosis of immunoreactive host cells and augmented donor leukocyte chimerism, not sustained inhibition of B7 molecule expression are associated with prolonged cardiac allograft survival in mice preconditioned with immature donor dendritic cells plus anti-CD40L mAb.
AU Lu L; Li W; Zhong C; Qian S; Fung J J; Thomson A W; Starzl T E
CS Thomas E. Starzl Transplantation Institute, and Department of Surgery,

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University of Pittsburgh, Pennsylvania 15213, USA.
NC AI41011 (NIAID)
DK 29961 (NIDDK)
DK49745 (NIDDK)
SO Transplantation, (1999 Sep 27) Vol. 68, No. 6, pp. 747-57.
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 5 Nov 1999
AB BACKGROUND: We previously reported the association among donor leukocyte chimerism, apoptosis of presumedly IL-2-deficient graft-infiltrating host cells, and the spontaneous donor-specific tolerance induced by liver but not heart allografts in mice. Survival of the rejection-prone heart allografts in the same strain combination is modestly prolonged by the pretransplant infusion of immature, costimulatory molecule-(CM) deficient donor dendritic cells (DC), an effect that is markedly potentiated by concomitant CM blockade with anti-CD40L (CD154) monoclonal antibody (mAb). We investigated whether the long survival of the heart allografts in the pretreated mice was associated with donor leukocyte chimerism and apoptosis of graft-infiltrating cells, if these end points were similar to those in the spontaneously tolerant liver transplant model, and whether the pretreatment effect was dependent on sustained inhibition of CM expression of the infused immature donor DC. In addition, apoptosis was assessed in the host spleen and lymph nodes, a critical determination not reported in previous studies of either spontaneous or "treatment-aided" organ tolerance models. METHODS: Seven days before transplantation of hearts from B10 (H-2b) donors, 2x10(6) donor-derived immature DC were infused i.v. into C3H (H-2k) recipient mice with or without a concomitant i.p. injection of anti-CD40L mAb. Donor cells were detected posttransplantation by immunohistochemical staining for major histocompatibility complex class II (I-Ab) in the cells of recipient lymphoid tissue. CM expression was determined by two-color labeling. Host responses to donor alloantigen were quantified by mixed leukocyte reaction, and cytotoxic T lymphocyte (CTL) assays. Apoptotic death in graft-infiltrating cells and in areas of T-dependent lymphoid tissue was visualized by terminal deoxynucleotidyltransferase-catalyzed dUTP-digoxigenin nick-end labeling and quantitative spectrofluorometry. Interleukin-2 production and localization were estimated by immunohistochemistry. RESULTS: Compared with control heart transplantation or heart transplantation after only DC administration, concomitant pretreatment with immature donor DC and anti-CD40L mAb caused sustained elevation of donor (I-Ab+) cells (microchimerism) in the spleen including T cell areas. More than 80% of the I-Ab+ cells in combined treatment animals also were CD86+, reflecting failure of the mAb to inhibit CD40/ CD80/CD86 up-regulation on immature DC in vitro after their interaction with host T cells. Donor-specific CTL activity in graft-infiltrating cells and spleen cell populations of these animals was present on day 8, but decreased strikingly to normal control levels by day 14. The decrease was associated with enhanced apoptosis of graft-infiltrating cells and of cells in the spleen where interleukin-2 production was inhibited. The highest levels of splenic microchimerism were found in mice with long surviving grafts (>100 days). In contrast, CTL activity was persistently elevated in control heart graft recipients with

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comparatively low levels of apoptotic activity and high levels of interleukin-2. CONCLUSION: The donor-specific acceptance of rejection-prone heart allografts by recipients pretreated with immature donor DC and anti-CD40L mAb is not dependent on sustained inhibition of donor DC CM (CD86) expression. Instead, the pretreatment facilitates a tolerogenic cascade similar to that in spontaneously tolerant liver recipients that involves: (1) chimerism-driven immune activation, succeeded by deletion of host immune responder cells by apoptosis in the spleen and allograft that is linked to interleukin-2 deficiency in both locations and (2) persistence of comparatively large numbers of donor-derived leukocytes. These tolerogenic mechanisms are thought to be generic, explaining the tolerance induced by allografts spontaneously, or with the aid of various kinds of immunosuppression.

CT Check Tags: Male
Animals
Antibodies, Monoclonal: PD, pharmacology
*Antigens, CD: BI, biosynthesis
Antigens, CD86
Antigens, Differentiation, T-Lymphocyte: IM, immunology
Apoptosis
Bone Marrow Cells: IM, immunology
CD40 Ligand
Dendritic Cells: CY, cytology
Dendritic Cells: IM, immunology
Dendritic Cells: ME, metabolism
Graft Survival: PH, physiology
Granulocyte-Macrophage Colony-Stimulating Factor: PD, pharmacology
*Heart Transplantation: IM, immunology
*Heart Transplantation: PA, pathology
Immunophenotyping
Interleukin-4: PD, pharmacology
Leukocyte Transfusion
*Lymphoid Tissue: CY, cytology
*Membrane Glycoproteins: BI, biosynthesis
*Membrane Glycoproteins: IM, immunology
Mice
Mice, Inbred BALB C
Mice, Inbred C3H
Mice, Inbred C57BL
Research Support, U.S. Gov't, P.H.S.
Spleen: CY, cytology
T-Lymphocytes, Cytotoxic: IM, immunology
Transforming Growth Factor beta: PD, pharmacology
*Transplantation Chimera: IM, immunology
*Transplantation Conditioning: MT, methods

RN 147205-72-9 (CD40 Ligand); 207137-56-2 (Interleukin-4); 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD); 0 (Antigens, CD86); 0 (Antigens, Differentiation, T-Lymphocyte); 0 (Cd86 protein, mouse); 0 (Membrane Glycoproteins); 0 (Transforming Growth Factor beta)

L11 ANSWER 9 OF 15 MEDLINE on STN
AN 1999426531 MEDLINE
DN PubMed ID: 10498243
TI Combination of CD80 and granulocyte-macrophage colony-stimulating factor coexpression by a leukemia cell vaccine: preclinical studies in a murine model recapitulating Philadelphia chromosome-positive acute lymphoblastic leukemia.

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AU Stripecke R; Skelton D C; Pattengale P K; Shimada H; Kohn D B
CS Division of Research Immunology/BMT, Childrens Hospital Los Angeles, CA 90027, USA.
SO Human gene therapy, (1999 Sep 1) Vol. 10, No. 13, pp. 2109-22.
Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 27 Oct 1999
AB Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) is a highly aggressive malignancy caused by the bcr-abl translocation oncogene. To explore alternative treatments for Ph+ ALL we tested gene-modified cell vaccines in the BALB/c-derived BM185 leukemia model. We compared the efficacy of BM185 cell vaccine expressing CD80 alone or in combination with IL-2 or GM-CSF. Mice injected with viable BM185 leukemia cells modified to express CD80 and GM-CSF (BM185/CD80+GM-CSF) showed the highest leukemia rejection rates. Cell vaccines consisting of irradiated BM185/CD80+GM-CSF cells administered subcutaneously stimulated a potent cytotoxic T lymphocyte (CTL) response against parental BM185. Histological examination of the vaccination site showed a large concentration of immune cells. Administration of the BM185/CD80+GM-CSF cell vaccine before intravenous challenge with parental cells caused strong inhibition of leukemia development. Vaccination after subcutaneous challenge with BM185 cells caused efficient elimination of leukemia promoting 40-60% long-term survival rates. The immunization efficacy of the BM185/CD80+ GM-CSF cell vaccine was directly correlated with the percentage of cells expressing the transgenes. In all, this preclinical study shows that leukemia cell vaccines coexpressing CD80 and GM-CSF can potentially be explored for immunotherapy in Ph+ ALL patients.
CT Check Tags: Male
Animals
Antigen-Presenting Cells: IM, immunology
*Antigens, CD80: ME, metabolism
Cancer Vaccines: ME, metabolism
Cancer Vaccines: RE, radiation effects
*Cancer Vaccines: TU, therapeutic use
Cell Line
Cytotoxicity, Immunologic
*Gene Therapy
Gene Transfer Techniques
*Granulocyte-Macrophage Colony-Stimulating Factor: ME, metabolism
Humans
Immunohistochemistry
Immunotherapy
Interleukin-2: ME, metabolism
Leukemia, Lymphocytic, Acute, L2: IM, immunology
*Leukemia, Lymphocytic, Acute, L2: TH, therapy
Mice
Mice, Inbred BALB C
Microscopy, Electron
Neoplasm Transplantation
Research Support, Non-U.S. Gov't
T-Lymphocytes, Cytotoxic: IM, immunology
RN 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

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CN 0 (Antigens, CD80); 0 (Cancer Vaccines); 0 (Interleukin -2)

L11 ANSWER 10 OF 15 MEDLINE on STN
AN 1999408755 MEDLINE
DN PubMed ID: 10477744
TI Stealth cells: prevention of major histocompatibility complex class II-mediated T-cell activation by cell surface modification.
AU Murad K L; Gosselin E J; Eaton J W; Scott M D
CS Division of Experimental Pathology, Department of Microbiology and Immunology, Albany Medical College, Albany, NY, USA.
NC AI35327 (NIAID)
HL53066 (NHLBI)
HL58584 (NHLBI)
SO Blood, (1999 Sep 15) Vol. 94, No. 6, pp. 2135-41.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199910
ED Entered STN: 26 Oct 1999
Last Updated on STN: 26 Oct 1999
Entered Medline: 12 Oct 1999
AB Transfusion or transplantation of T lymphocytes into an allogeneic recipient can evoke potent immune responses including, in immunocompromised patients, graft-versus-host disease (GVHD). As our previous studies demonstrated attenuated immunorecognition of red blood cells covalently modified with methoxy(polyethylene glycol) (mPEG), we hypothesized that T-cell activation by foreign antigens might similarly be prevented by mPEG modification. Mixed lymphocyte reactions (MLR) using peripheral blood mononuclear cells (PBMC) from HLA class II disparate donors demonstrate that mPEG modification of PBMC effectively inhibits T-cell proliferation (measured by (3)H-thymidine incorporation) in a dose-dependent manner. Even slight derivatization (0.4 mmol/L mPEG per 4 x 10(6) cells) resulted in a >/=75% decrease, while higher concentrations caused >/=96% decrease in proliferation. Loss of PBMC proliferation was not due to either mPEG-induced cytotoxicity, as viability was normal, or cellular anergy, as phytohemagglutinin (PHA)-stimulated mPEG-PBMC demonstrated normal proliferative responses. Addition of exogenous interleukin (IL)-2 also had no proliferative effect, suggesting that the mPEG-modified T cells were not antigen primed. Flow cytometric analysis demonstrates that mPEG-modification dramatically decreases antibody recognition of multiple molecules involved in essential cell:cell interactions, including both T-cell molecules (CD2, CD3, CD4, CD8, CD28, CD11a, CD62L) and antigen-presenting cell (APC) molecules (CD80, CD58, CD62L) likely preventing the initial adhesion and costimulatory events necessary for immune recognition and response.
CT *Antigen-Presenting Cells: IM, immunology
Antigens, CD: AN, analysis
Blood Donors
Cells, Cultured
Erythrocytes: IM, immunology
Flow Cytometry
*HLA-D Antigens: IM, immunology
Humans
Immunophenotyping
Interleukin-2: PD, pharmacology
*Lymphocyte Activation: DE, drug effects

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Lymphocyte Activation: IM, immunology
Lymphocyte Culture Test, Mixed
*Polyethylene Glycols: PD, pharmacology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
T-Lymphocytes: DE, drug effects
*T-Lymphocytes: IM, immunology
RN 9004-74-4 (monomethoxypolyethylene glycol)
CN 0 (Antigens, CD); 0 (HLA-D Antigens); 0 (Interleukin-2); 0 (Polyethylene Glycols)

L11 ANSWER 11 OF 15 MEDLINE on STN
AN 97102408 MEDLINE
DN PubMed ID: 8946835
TI Defective post-thymic tolerance mechanisms during the chronic progressive stage of multiple sclerosis.
AU Correale J; Gilmore W; Lopez J; Li S Q; McMillan M; Weiner L P
CS Department of Neurology, University of Southern California, School of Medicine, Los Angeles 90033, USA.
SO Nature medicine, (1996 Dec) Vol. 2, No. 12, pp. 1354-60.
Journal code: 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 7 Jan 1997
AB We have recently isolated a panel of T-cell clones from chronic progressive multiple sclerosis (MS) patients that are capable of functioning as antigen-presenting cells and of expressing the costimulatory molecules B7-1 and B7-2. In this report we show that these T-cell clones are resistant to inhibitory regulation, including the induction of anergy and sensitivity to tumor growth factor-beta (TGF-beta)-induced growth inhibition. The resistance to anergy induction was associated with expression of B7 costimulatory molecules. These data suggest that lack of responsiveness to peripheral inhibitory signals may account for the entry of autoimmune diseases into a chronic progressive phase.
CT Check Tags: Female; Male
Adult
Antibodies, Monoclonal
Antigen-Presenting Cells: IM, immunology
Antigens, CD80: IM, immunology
Cell Division: DE, drug effects
Chronic Disease
*Clonal Anergy
Histocompatibility Testing
Humans
Interferon Type II: BI, biosynthesis
Interleukin-2: GE, genetics
Interleukin-4: BI, biosynthesis
Middle Aged
*Multiple Sclerosis: IM, immunology
Myelin Proteolipid Protein: IM, immunology
RNA, Messenger: AN, analysis
Receptors, Antigen, T-Cell, alpha-beta: IM, immunology
Research Support, Non-U.S. Gov't

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*T-Lymphocytes: IM, immunology
Transforming Growth Factor beta: PD, pharmacology
RN 207137-56-2 (Interleukin-4); 82115-62-6 (Interferon Type II)
CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD80); 0 (Interleukin-2); 0 (Myelin Proteolipid Protein); 0 (RNA, Messenger); 0 (Receptors, Antigen, T-Cell, alpha-beta); 0 (Transforming Growth Factor beta)

L11 ANSWER 12 OF 15 MEDLINE on STN
AN 95394042 MEDLINE
DN PubMed ID: 7545119
TI Tumor cells cotransfected with interleukin-7 and B7.1 genes induce CD25 and CD28 on tumor-infiltrating T lymphocytes and are strong vaccines.
AU Cayeux S; Beck C; Aicher A; Dorken B; Blankenstein T
CS Max-Delbruck-Center for Molecular Medicine, Berlin, Germany.
SO European journal of immunology, (1995 Aug) Vol. 25, No. 8, pp. 2325-31.
Journal code: 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 20 Oct 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 10 Oct 1995
AB Interleukin-7 (IL-7) and the membrane molecule B7 are both able to provide proliferation and activation signals for T cells. However, tumor cells transfected to express either molecule alone are not reliably rejected in syngeneic hosts or are not sufficiently immunogenic to serve as potent tumor vaccines. Since IL-7 and B7 have shown synergistically to induce activation and proliferation of T cells in vitro, we have expressed B7.1 by means of a retrovirus in the mammary adenocarcinoma TS/A which arose spontaneously in a BALB/c mouse and in the plasmacytoma J558L and their IL-7-transfected sublines to improve vaccine efficacy. Expression of IL-7 or B7.1 alone in tumor cells decreased tumorigenicity, but nevertheless tumors grew in a substantial number of mice. In contrast, IL-7/B7.1 cotransfected cells did not grow as tumor in a single case. This inhibition of tumor growth was completely T cell dependent, because TS/A-IL-7/B7.1 cells retained their full tumorigenic potential in T cell-deficient mice. Analysis of tumor-infiltrating T lymphocytes revealed increased numbers of T cells in B7, IL-7 and IL-7/B7 transfected compared to parental tumors. In IL-7/B7 transfected tumors, T cell numbers were not further increased compared to that in single-gene-transfected tumors. However, T cells in B7 and IL-7 transfected tumors differed phenotypically with respect to activation markers. In B7 transfected tumors, T cells were predominantly CD28+ and CD25-, while in IL-7 transfected tumors, T cells were mainly CD28- and CD25+. In IL-7/B7 cotransfected tumors, the majority of T cells was CD28+ and CD25+. Thus, IL-7 and B7 induced an anti-tumor immune response by complementary T cell directed pathways in a cooperative fashion. Importantly, immunization of mice with the transfected cells and subsequent contralateral challenge with parental tumor cells showed that IL-7/B7 co-expressing cells induced the most strongly protective immunity, which is superior to that induced by single-gene transfectants and to the adjuvant Corynebacterium parvum. Vaccine efficacy was abrogated when irradiated cells were used for vaccination. Together, our results show that IL-7 and B7.1 transfected tumor cells induce strong T cell activation and tumor immunity.

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50613257

CT Check Tags: Female
Animals
*Antigens, CD28: BI, biosynthesis
*Antigens, CD80: GE, genetics
Cryptosporidium parvum: IM, immunology
*Interleukin-7: GE, genetics
*Lymphocytes, Tumor-Infiltrating: ME, metabolism
Mice
Mice, Inbred BALB C
Mice, Nude
Mice, SCID
Neoplasm Transplantation: IM, immunology
*Receptors, Interleukin-2: BI, biosynthesis
Research Support, Non-U.S. Gov't
Transfection: GE, genetics
Tumor Cells, Cultured
Vaccines, Synthetic: GE, genetics
CN 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Interleukin-7); 0 (Receptors, Interleukin-2); 0 (Vaccines, Synthetic)

L11 ANSWER 13 OF 15 MEDLINE on STN
AN 95286844 MEDLINE
DN PubMed ID: 7539461
TI Long-term inhibition of murine experimental autoimmune encephalomyelitis using CTLA-4-Fc supports a key role for CD28 costimulation.
AU Cross A H; Girard T J; Giacoletto K S; Evans R J; Keeling R M; Lin R F; Trotter J L; Karr R W
CS Department of Neurology and Neurosurgery, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
SO The Journal of clinical investigation, (1995 Jun) Vol. 95, No. 6, pp. 2783-9.
Journal code: 7802877. ISSN: 0021-9738.
CM Comment in: J Clin Invest. 1995 Jun;95(6):2429-30. PubMed ID: 7539451
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199507
ED Entered STN: 13 Jul 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 6 Jul 1995
AB T cell activation involves not only recognition of antigen presented by the MHC, but also nonspecific interactions termed "costimulation." The costimulatory molecules B7-1 and B7-2 are ligands on antigen-presenting cells for the CD28 and CTLA-4 receptors on T cells. Previously, a fusion protein consisting of human CTLA-4 linked to human Fc was shown to bind B7-1 and B7-2 with high avidity and to prevent specific T cell activation. Here we investigated the effects of a recombinant fusion protein consisting of the extracellular domain of human CTLA-4 bound to mouse IgG2a Fc (CTLA-4-Fc) upon experimental autoimmune encephalomyelitis, a T cell-mediated disease that serves as a model for multiple sclerosis. CTLA-4-Fc prevented experimental autoimmune encephalomyelitis in 26 of 28 CTLA-4-Fc-treated mice (median maximum score 0), whereas 28 of 30 mice treated with control mouse IgG2a developed disease (median maximum score 2.75). Less inflammation and virtually no demyelination or axonal loss occurred in CTLA-4-Fc-treated compared with control-treated mice. Activated splenocytes from CTLA-4-Fc-treated mice were able to transfer disease adoptively to naive recipients. These

results indicate a key role for the B7/CD28 system in the development of actively induced murine experimental autoimmune encephalomyelitis, suggesting an area of investigation with therapeutic potential for multiple sclerosis.

CT Check Tags: Female
Animals
*Antigens, CD28: PH, physiology
*Antigens, CD80: PH, physiology
*Antigens, Differentiation: CH, chemistry
Antigens, Differentiation: PD, pharmacology
Base Sequence
DNA Primers: CH, chemistry
Encephalomyelitis, Autoimmune, Experimental: PA, pathology
*Encephalomyelitis, Autoimmune, Experimental: PC, prevention & control
*Immunoconjugates
Immunoglobulin Fc Fragments: CH, chemistry
Immunoglobulin Fc Fragments: PD, pharmacology
Interleukin-2: ME, metabolism
Lymphocyte Activation
Mice
Mice, Inbred Strains
Molecular Sequence Data
Multiple Sclerosis: IM, immunology
Recombinant Fusion Proteins
Research Support, Non-U.S. Gov't
Spinal Cord: PA, pathology
*T-Lymphocytes: IM, immunology
Time Factors

CN 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (DNA Primers); 0 (Immunoconjugates); 0 (Immunoglobulin Fc Fragments); 0 (Interleukin-2); 0 (Recombinant Fusion Proteins); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L11 ANSWER 14 OF 15 MEDLINE on STN
AN 95239129 MEDLINE
DN PubMed ID: 7536798
TI CD28-B7 blockade after alloantigenic challenge in vivo inhibits Th1 cytokines but spares Th2.
AU Sayegh M H; Akalin E; Hancock W W; Russell M E; Carpenter C B; Linsley P S; Turka L A
CS Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
NC R01 AI-33100-03 (NIAID)
R29 AI-349965-01 (NIAID)
SO The Journal of experimental medicine, (1995 May 1) Vol. 181, No. 5, pp. 1869-74.
Journal code: 2985109R. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199505
ED Entered STN: 5 Jun 1995
Last Updated on STN: 29 Jan 1996
Entered Medline: 25 May 1995
AB Blocking the CD28-B7 T cell costimulatory pathway with the fusion protein CTLA4Ig inhibits alloimmune responses in vitro and in vivo and induces tolerance to cardiac allografts in mice and rats, but the mechanisms mediating the tolerant state in vivo are unknown. Here, we

report the effects and potential mechanisms of CTLA4Ig in the rat renal allograft model. LEW rats were nephrectomized and received renal allografts from major histocompatibility complex-incompatible WF rats. While all untreated and control immunoglobulin (Ig)-treated animals acutely rejected their allografts and died, 86% of rats that received a single injection of CTLA4Ig on day 2 after transplantation had prolonged survival (> 60-100 days) with preserved renal function. By contrast, only 29% of animals that received CTLA4Ig on the day of engraftment had prolonged survival. Long-term survivors (> 100 days) exhibited donor-specific tolerance, accepting donor-matched WF but acutely rejecting third-party BN cardiac allografts. Immunohistological analysis of grafts sampled at 1 week after transplantation showed that both control and CTLA4Ig-treated animals had mononuclear cell infiltrates, with a higher percentage of CD4+ cells in the CTLA4Ig-treated group. However, while this was associated with vasculitis and tubulitis in control grafts, there was no evidence of tissue injury in CTLA4Ig-treated animals. The immune response leading to graft rejection in control animals was characterized by expression of the T helper (Th) type 1 cytokines interleukin (IL)-2 and interferon-gamma. In contrast, the persistent CD4+ infiltrate without graft rejection in CTLA4Ig-treated animals was associated with increased staining for the Th2-related cytokines IL-4 and IL-10. Furthermore, grafts from CTLA4Ig-treated animals had marked upregulation of intragraft staining for IgG1, but not IgG2a or IgG2b. Administration of rIL-2 to CTLA4Ig-treated animals restored allograft rejection in 50% of animals tested. These results confirm that blockade of the CD28-B7 pathway after alloantigenic challenge induces donor-specific acceptance of vascularized organ allografts, and indicates in this model that CTLA4Ig inhibits Th1 but spares Th2 cytokines in vivo.

CT Check Tags: Male
Animals
*Antigens, CD28: PH, physiology
*Antigens, CD80: PH, physiology
Antigens, Differentiation: IM, immunology
*Cytokines: BI, biosynthesis
Immune Tolerance
*Immunoconjugates
Interleukin-2: PD, pharmacology
*Isoantigens: IM, immunology
Kidney Transplantation
Rats
Rats, Inbred BN
Rats, Inbred Lew
Research Support, U.S. Gov't, P.H.S.
*Th1 Cells: PH, physiology
*Th2 Cells: PH, physiology
Transplantation, Homologous

CN 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (Cytokines); 0 (Immunoconjugates); 0 (Interleukin-2); 0 (Isoantigens); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L11 ANSWER 15 OF 15 MEDLINE on STN
AN 95053698 MEDLINE
DN PubMed ID: 7525835
TI CD2 is involved in maintenance and reversal of human alloantigen-specific clonal anergy.
AU Boussiotis V A; Freeman G J; Griffin J D; Gray G S; Gribben J G; Nadler L M

Erich Leeser

50613257

CS Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115.
NC CA-34183 (NCI)
CA-40416 (NCI)
SO The Journal of experimental medicine, (1994 Nov 1) Vol. 180, No. 5, pp. 1665-73.
Journal code: 2985109R. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
ED Entered STN: 10 Jan 1995
Last Updated on STN: 29 Jan 1996
Entered Medline: 1 Dec 1994
AB Induction and maintenance of a state of T cell unresponsiveness to specific alloantigen would have significant implications for human organ transplantation. Using human histocompatibility leukocyte antigen DR7-specific helper T cell clones, we demonstrate that blockade of the B7 family of costimulatory molecules is sufficient to induce alloantigen-specific T cell clonal anergy. Anergized cells do not respond to alloantigen and a variety of costimulatory molecules, including B7-1, B7-2, intercellular adhesion molecule-1 (ICAM-1), and lymphocyte function-associated molecule (LFA)-3. However, after culture in exogenous interleukin (IL)-2 for at least 7 d, anergized cells can respond to alloantigen in the presence of LFA-3. LFA-3 costimulation subsequently restores responsiveness to alloantigen in the presence of previously insufficient costimulatory signals. Expression of CD2R epitope is downregulated on anergic cells and is restored after 7 d of IL-2 culture. The loss of the CD2R is temporally associated with the inability of anergized cells to respond to LFA-3. These results suggest that in addition to blockade of B7 family members, inhibition of CD2 and, potentially, other costimulatory pathways that might reverse anergy will be necessary to maintain prolonged alloantigen-specific tolerance.
CT Antigens, CD: PH, physiology
*Antigens, CD2: PH, physiology
Antigens, CD58
Antigens, CD80: PH, physiology
Antigens, Differentiation: PH, physiology
*Clonal Anergy
Clone Cells
Epitopes
HLA-DR7 Antigen: PH, physiology
Humans
*Immunoconjugates
Interleukin-2: PD, pharmacology
*Isoantigens: IM, immunology
Membrane Glycoproteins: PH, physiology
Research Support, U.S. Gov't, P.H.S.
CN 0 (Antigens, CD); 0 (Antigens, CD2); 0 (Antigens, CD58); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (Epitopes); 0 (HLA-DR7 Antigen); 0 (Immunoconjugates); 0 (Interleukin-2); 0 (Isoantigens); 0 (Membrane Glycoproteins); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

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STN TRANSCRIPT FOR SN 10/547,448

50613257

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptaeal1624

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	OCT 23	The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded
NEWS 4	OCT 30	CHEMLIST enhanced with new search and display field
NEWS 5	NOV 03	JAPIO enhanced with IPC 8 features and functionality
NEWS 6	NOV 10	CA/CAplus F-Term thesaurus enhanced
NEWS 7	NOV 10	STN Express with Discover! free maintenance release Version 8.01c now available
NEWS 8	NOV 20	CAS Registry Number crossover limit increased to 300,000 in additional databases
NEWS 9	NOV 20	CA/CAplus to MARPAT accession number crossover limit increased to 50,000
NEWS 10	DEC 01	CAS REGISTRY updated with new ambiguity codes
NEWS 11	DEC 11	CAS REGISTRY chemical nomenclature enhanced
NEWS 12	DEC 14	WPIDS/WPINDEX/WPIX manual codes updated
NEWS 13	DEC 14	GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS 14	DEC 18	CA/CAplus pre-1967 chemical substance index entries enhanced with preparation role
NEWS 15	DEC 18	CA/CAplus patent kind codes updated
NEWS 16	DEC 18	MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS 17	DEC 18	MEDLINE updated in preparation for 2007 reload
NEWS 18	DEC 27	CA/CAplus enhanced with more pre-1907 records
NEWS 19	JAN 08	CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 20	JAN 16	CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 21	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS 22	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 16:25:37 ON 19 JAN 2007

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 16:26:10 ON 19 JAN 2007

FILE LAST UPDATED: 18 Jan 2007 (20070118/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> interleukin 2
INTERLEUKIN IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s interleukin 2
        152500 INTERLEUKIN
          7830 INTERLEUKINS
        155212 INTERLEUKIN
                  (INTERLEUKIN OR INTERLEUKINS)
       3428005 2
L1       43940 INTERLEUKIN 2
                  (INTERLEUKIN(W)2)

=> l1 or IL2
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l1 or IL2
          2028 IL2
L2       44423 L1 OR IL2

=> s l2 and inhibition
        447324 INHIBITION
          3172 INHIBITIONS
        448716 INHIBITION
                  (INHIBITION OR INHIBITIONS)
L3        4254 L2 AND INHIBITION
```

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50613257

```
=> s l3 and review
        466169 REVIEW
         58417 REVIEWS
        511113 REVIEW
                  (REVIEW OR REVIEWS)
L4          25 L3 AND REVIEW

=> s l4 and CD80/CD28
'CD28' IS NOT A VALID FIELD CODE
            0 CD80/CD28
L5          0 L4 AND CD80/CD28

=> s l4 and CD80
         4712 CD80
L6          1 L4 AND CD80

=> s l5 full
'CD28' IS NOT A VALID FIELD CODE
            0 CD80/CD28
L7          0 L4 AND CD80/CD28

=> s l6 full
         4712 CD80
L8          1 L4 AND CD80

=> d l8

L8   ANSWER 1 OF 1     MEDLINE on STN
AN   97302693     MEDLINE
DN   PubMed ID: 9158940
TI   Cytokine-based gene therapy of human tumors. An overview.
AU   Parmiani G; Arienti F; Sule-Suso J; Melani C; Colombo M P; Ramakrishna V;
     Belli F; Mascheroni L; Rivoltini L; Cascinelli N
CS   Division of Experimental Oncology D, Instituto Nazionale Tumori, Milan,
     Italy.
SO   Folia biologica, (1996) Vol. 42, No. 6, pp. 305-9.  Ref: 21
     Journal code: 0234640. ISSN: 0015-5500.
CY   Czech Republic
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
LA   English
FS   Priority Journals
EM   199707
ED   Entered STN: 21 Jul 1997
     Last Updated on STN: 21 Jul 1997
     Entered Medline: 10 Jul 1997


=> FIL STNGUIDE
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               2.12       2.33

FILE 'STNGUIDE' ENTERED AT 16:29:27 ON 19 JAN 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
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FILE CONTAINS CURRENT INFORMATION.
```

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50613257

LAST RELOADED: Jan 12, 2007 (20070112/UP).

=> s l8 ibib abs hitstr tot
MISSING OPERATOR L8 IBIB
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l8 ibib abs hitstr tot
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE' - CONTINUE? (Y)/N:y

'HITSTR' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM,
ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and
PY.

To display a particular field or fields, enter the display field
codes. For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>). Examples of formats include: 'BIB';
'AB'; 'SO,ST'. You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be
used with the DISPLAY ACC command to display the record for a
specified Accession Number.
ENTER DISPLAY FORMAT (BIB):bib

L8 ANSWER 1 OF 1 MEDLINE on STN
AN 97302693 MEDLINE
DN PubMed ID: 9158940
TI Cytokine-based gene therapy of human tumors. An overview.
AU Parmiani G; Arienti F; Sule-Suso J; Melani C; Colombo M P; Ramakrishna V;
Belli F; Mascheroni L; Rivoltini L; Cascinelli N
CS Division of Experimental Oncology D, Instituto Nazionale Tumori, Milan,
Italy.
SO Folia biologica, (1996) Vol. 42, No. 6, pp. 305-9. Ref: 21

Erich Leeser

50613257

Journal code: 0234640. ISSN: 0015-5500.
CY Czech Republic
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 21 Jul 1997
Last Updated on STN: 21 Jul 1997
Entered Medline: 10 Jul 1997

=> FIL MEDLINE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	3.13

FILE 'MEDLINE' ENTERED AT 16:32:16 ON 19 JAN 2007

FILE LAST UPDATED: 18 Jan 2007 (20070118/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> DIS L8 1 IBIB ABS

L8 ANSWER 1 OF 1 MEDLINE on STN
ACCESSION NUMBER: 97302693 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9158940
TITLE: Cytokine-based gene therapy of human tumors. An overview.
AUTHOR: Parmiani G; Arienti F; Sule-Suso J; Melani C; Colombo M P; Ramakrishna V; Belli F; Mascheroni L; Rivoltini L; Cascinelli N
CORPORATE SOURCE: Division of Experimental Oncology D, Instituto Nazionale Tumori, Milan, Italy.
SOURCE: Folia biologica, (1996) Vol. 42, No. 6, pp. 305-9. Ref: 21
Journal code: 0234640. ISSN: 0015-5500.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 21 Jul 1997
Last Updated on STN: 21 Jul 1997
Entered Medline: 10 Jul 1997
AB This review first summarizes the different strategies of gene therapy of cancer and then focuses on the immunological approach. Several studies in animal models with cytokine gene-transduced tumor cells indicate that local cytokine release usually results in tumor growth inhibition. Moreover, in a number of cases vaccination with such cells can reduce growth of established tumors or even cure the tumor-bearing animals. Translation of such a principle in human clinical

Erich Leeser

50613257

setting is reported. We have transduced human melanoma cells with genes coding for interleukin (IL)-2, IL-4 or B7-1 and characterized such lines. The phenotype did not change after gene insertion but the functional, immunostimulatory activity of IL-2 or B7-1 gene-transduced melanoma cells was significantly increased compared to that of parental lines. These-lines were then used to vaccinate melanoma patients. Preliminary results of trials with IL-2 gene-transduced cells are presented which indicate a weak clinical response and the activation of a melanoma-specific cytotoxic T lymphocyte response in a low percentage of patients.

```
=> l2 and CD80
L2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l2 and CD80
          4712 CD80
L9         578 L2 AND CD80

=> s l9 and CD28
          5840 CD28
L10        261 L9 AND CD28

=> s l10 and CD80/CD28
'CD28' IS NOT A VALID FIELD CODE
             0 CD80/CD28
L11          0 L10 AND CD80/CD28

=> s l10 and autoimmune disease
         80683 AUTOIMMUNE
            42 AUTOIMMUNES
         80683 AUTOIMMUNE
                 (AUTOIMMUNE OR AUTOIMMUNES)
       1853615 DISEASE
       1688360 DISEASES
       3091773 DISEASE
                 (DISEASE OR DISEASES)
         46205 AUTOIMMUNE DISEASE
                 (AUTOIMMUNE(W)DISEASE)
L12         14 L10 AND AUTOIMMUNE DISEASE

=> d l12 full
'FULL' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
```

Erich Leeser

50613257

IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):bib

L12 ANSWER 1 OF 14 MEDLINE on STN
AN 2004556430 MEDLINE
DN PubMed ID: 15528977
TI Inhibition of lymphocyte activation and function by the prenylation inhibitor L-778,123.
AU Si Ming-Sing; Reitz Bruce A; Borie Dominic C
CS Transplantation Immunology Laboratory, Department of Cardiothoracic Surgery, Falk Cardiovasular Research Center, Stanford University School of Medicine, Stanford, CA 95305-5407, USA.
NC 1F32AI051094 (NIAID)
SO Investigational new drugs, (2005 Jan) Vol. 23, No. 1, pp. 21-9. Journal code: 8309330. ISSN: 0167-6997.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200506
ED Entered STN: 6 Nov 2004
Last Updated on STN: 3 Jun 2005
Entered Medline: 2 Jun 2005

=> d ibib abs hitstr 1-14
'HITSTR' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED

Erich Leeser

50613257

```
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms
```

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.

```
ENTER DISPLAY FORMAT (BIB):d ibib abs 1-14
'D' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'
```

The following are valid formats:

The default display format is BIB.

```
ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms
```

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the

Erich Leeser

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format specification.

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DALL --- ALL, delimited for post processing
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IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
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TRIAL -- TI, ST, CT, NA, RN, CN, GEN
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HITIND - IND
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The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
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IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):abs

L12 ANSWER 1 OF 14 MEDLINE on STN
AB Prenylated Ras GTPases transduce signals from the T cell receptor, CD28 costimulatory receptor and IL-2 receptor. Since signals from these receptors mediate T cell activation, proliferation and survival, we hypothesized that the prenylation inhibitor L-778,123 would impart immunomodulation.The effect of L-778,123 on T cell activation (CD71 or CD25 surface expression) was determined by flow cytometry. Peripheral blood mononuclear cell (PBMC) proliferation in the presence of L-778,123 and/or cyclosporine (CsA) was determined by [3H]thymidine incorporation. The ability of L-778,123 to inhibit IL-2 receptor signaling was investigated by measuring IL-2 induced proliferation in CTLL-2 cells and IL-2 prevention of apoptosis in activated human PBMC. L-778,123 inhibited lectin induced expression of CD71 and CD25 with IC50's of 6.48 +/- 1.31 microM and 84.1 +/- 50.0 microM, respectively. PBMC proliferation was inhibited by L-778,123 with an IC50 of 0.92 +/- 0.23 microM, and addition of CsA did not increase the potency. L-778,123 did not inhibit IL-2 and IFN-gamma production by T cells. L-778,123 abrogated IL-2 induced proliferation of CTLL-2 cells with an IC50 of 0.81 +/- 0.44 microM. However, L-778,123 minimally reversed the prosurvival effect of IL-2 in activated lymphocytes. IL-2 ligand and receptor production during T cell activation are relatively unaffected by L-778,123. However, the activation and proliferative effects of IL-2 on T cells are potently blocked by L-778,123. These results reveal a selective blockade of the IL-2 cytokine axis distal to the IL-2 receptor by the L-778,123 and warrant evaluation of prenylation inhibitors in treating transplant rejection and autoimmune diseases.

L12 ANSWER 2 OF 14 MEDLINE on STN
AB CD28/B7 blockade leads to exacerbated autoimmune disease in the nonobese diabetic mouse strain as a result of a marked reduction in the number of CD4(+)CD25(+) regulatory T cells (Tregs). Herein, we demonstrate that CD28 controls both thymic development and peripheral homeostasis of Tregs. CD28 maintains a stable pool of peripheral Tregs by both supporting their survival and promoting their self-renewal. CD28 engagement promotes survival

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by regulating IL-2 production by conventional T cells and CD25 expression on Tregs.

L12 ANSWER 3 OF 14 MEDLINE on STN
AB Programmed death-1 (PD-1) is an immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing receptor expressed upon T cell activation. PD-1(-/-) animals develop autoimmune diseases, suggesting an inhibitory role for PD-1 in immune responses. Members of the B7 family, PD-L1 and PD-L2, are ligands for PD-1. This study examines the functional consequences of PD-1:PD-L engagement on murine CD4 and CD8 T cells and shows that these interactions result in inhibition of proliferation and cytokine production. T cells stimulated with anti-CD3/PD-L1.Fc-coated beads display dramatically decreased proliferation and IL-2 production, while CSFE analysis shows fewer cells cycling and a slower division rate. Costimulation with soluble anti-CD28 mAb can overcome PD-1-mediated inhibition by augmenting IL-2 production. However, PD-1:PD-L interactions inhibit IL-2 production even in the presence of costimulation and, thus, after prolonged activation, the PD-1:PD-L inhibitory pathway dominates. Exogenous IL-2 is able to overcome PD-L1-mediated inhibition at all times, indicating that cells maintain IL-2 responsiveness. Experiments using TCR transgenic CD4(+) or CD8(+) T cells stimulated with antigen-presenting cells expressing PD-L1 show that both T cell subsets are susceptible to this inhibitory pathway. However, CD8(+) T cells may be more sensitive to modulation by the PD-1:PD-L pathway because of their intrinsic inability to produce significant levels of IL-2.

L12 ANSWER 4 OF 14 MEDLINE on STN
AB The need for permanent, nonspecific, and potentially harmful immunosuppression remains a major obstacle for islet transplantation. The response of a type 1 diabetic recipient to an islet graft includes a specific allogenic immune response and the recurrence of autoimmunity. Free or encapsulated in an immunoisolation device, islet cells are exposed to immune aggression, initiated by donor antigen-presenting cells or by indirect, host antigen-presenting cell-mediated antigen presentation. CTLA4-Ig is a genetically engineered fusion protein of human CTLA4 and the IgG 1 Fc region. It prevents T-cell activation by binding to human B7, which costimulates T cells through CD28. Interesting data were reported in experimental islet transplantation, suggesting that CTLA4-Ig may be slightly but significantly beneficial to islet allograft survival, although studies in autoimmune diabetes are scarce. The main limitations include transient and low levels of expression when CTLA4-Ig is delivered locally, a predominant effect on the direct recognition pathway, and the lack of effect on memory cells. Clinical trials in islet transplantation could be discussed in nonuremic patients, with steroid-free and anticalcineurin-free regimens, in combination with another costimulation blocker, rapamycin, and an anti-interleukin 2 receptor antibody, and with a strategy directed against the recurrence of autoimmunity.

L12 ANSWER 5 OF 14 MEDLINE on STN
AB Depletion of the minor (approximately 10%) subpopulation of CD4+ T cells that co-expresses CD25 (interleukin (IL)-2 receptor alpha-chain) by thymectomy of neonates on the third day of life or by treatment of adult CD4+ T cells with anti-CD25 and complement results in the development of organ-specific autoimmunity. Autoimmune disease can be prevented by reconstitution of the animals with CD4+ CD25+ cells. CD4+ CD25+-mediated protection of autoimmune gastritis does not require the suppressor cytokines IL-4, IL-10, or transforming growth factor

(TGF)-beta. Mice that express a transgenic T-cell receptor (TCR) derived from a thymectomized newborn that recognizes the gastric parietal cell antigen H/K ATPase all develop severe autoimmune gastritis very early in life. CD4+ CD25+ T cells are also powerful suppressors of the activation of both CD4+ and CD8+ T cells in vitro. Suppression is mediated by a cell contact-dependent, cytokine-independent T-T interaction. Activation of CD4+ CD25+ via their TCR generates suppressor effector cells that are capable of non-specifically suppressing the activation of any CD4+ or CD8+ T cell. Activation of suppressor effector function is independent of co-stimulation mediated by CD28/CTLA-4 interactions with CD80/CD86. We propose that CD4+ CD25+ T cells recognize organ-specific antigens, are recruited to sites of autoimmune damage where they are activated by their target antigen, and then physically interact with autoreactive CD4+ or CD8+ effector cells to suppress the development of autoimmune disease.

L12 ANSWER 6 OF 14 MEDLINE on STN

AB We recently reported that CD47 ligation inhibited IL-2 release by umbilical cord blood mononuclear cells activated in the presence of IL-12, but not IL-4, preventing the induction of IL-12Rbeta(2) expression and the acquisition of Th1, but not the Th2 phenotype. Here we show that in the absence of exogenous cytokine at priming, CD47 ligation of umbilical cord blood mononuclear cells promotes the development of hyporesponsive T cells. Naive cells were treated with CD47 mAb for 3 days, expanded in IL-2 for 9-12 days, and restimulated by CD3 and CD28 coengagement. Effector T cells generated under these conditions were considered to be anergic because they produced a reduced amount of IL-2 at the single-cell level and displayed an impaired capacity 1) to proliferate, 2) to secrete Th1/Th2 cytokines, and 3) to respond to IL-2, IL-4, or IL-12. Moreover, CD47 mAb strongly suppressed IL-2 production and IL-2Ralpha expression in primary cultures and IL-2 response of activated naive T cells. Induction of anergy by CD47 mAb was IL-10 independent, whereas inclusion of IL-2 and IL-4, but not IL-7, at priming fully restored T cell activation. Furthermore, CD28 costimulation prevented induction of anergy. Thus, CD47 may represent a potential target to induce anergy and prevent undesired Th0/Th1 responses such as graft vs host diseases, allograft rejection, or autoimmune diseases.

L12 ANSWER 7 OF 14 MEDLINE on STN

AB Thymectomy in mice on neonatal day 3 leads to the development of multiorgan autoimmune disease due to loss of a CD(+)CD25(+) T cell regulatory population in their peripheral lymphoid tissues. Here, we report the identification of a CD4(+) population of regulatory T cells in the circulation of humans expressing high levels of CD25 that exhibit in vitro characteristics identical with those of the CD4(+)CD25(+) regulatory cells isolated in mice. With TCR cross-linking, CD4(+)CD25(high) cells did not proliferate but instead totally inhibited proliferation and cytokine secretion by activated CD4(+)CD25(-) responder T cells in a contact-dependent manner. The CD4(+)CD25(high) regulatory T cells expressed high levels of CD45RO but not CD45RA, akin to the expression of CD45RB(low) on murine CD4(+)CD25(+) regulatory cells. Increasing the strength of signal by providing either costimulation with CD28 cross-linking or the addition of IL-2 to a maximal anti-CD3 stimulus resulted in a modest induction of proliferation and the loss of observable suppression in cocultures of CD4(+)CD25(high) regulatory cells and CD4(+)CD25(-) responder cells. Whereas higher ratios of CD4(+)CD25(high) T cells are required to suppress proliferation if the PD-L1 receptor is blocked, regulatory cell function is shown to persist in

the absence of the PD-1/PD-L1 or CTLA-4/B7 pathway. Thus, regulatory CD4 T cells expressing high levels of the IL-2 receptor are present in humans, providing the opportunity to determine whether alterations of these populations of T cells are involved in the induction of human autoimmune disorders.

L12 ANSWER 8 OF 14 MEDLINE on STN
AB It has been reported that costimulation blockade can result in T cell anergy. We investigated the effects of blocking costimulatory molecules in vivo on the development of experimental autoimmune uveoretinitis (EAU), a model for autoimmune uveitis in humans that is induced in mice by immunization with the retinal Ag interphotoreceptor retinoid binding protein. B10.A mice immunized with a uveitogenic regimen of interphotoreceptor retinoid-binding protein were treated with Abs to B7.1 and B7.2 for 2 wk. Evaluation of EAU and immunological responses 1 wk later showed that disease had been abrogated, and cellular responses were suppressed. To determine whether the costimulation blockade resulted in tolerance, adult-thymectomized mice immunized for uveitis and treated with anti-B7 or anti-CD28 were rechallenged for uveitis induction 5 wk after the initial immunization. Although confirmed to be disease free after the initial immunization, both anti-B7- and anti-CD28 -treated mice developed severe EAU and elevated cellular responses after the rechallenge, equivalent to those of control mice. We conclude that in this model costimulatory blockade in vivo prevents the development of autoimmune disease, but does not result in long-term tolerance. The data are compatible with the interpretation that B7/ CD28 blockade prevents generation of effector, but not of memory, T cells.

L12 ANSWER 9 OF 14 MEDLINE on STN
AB CD28/B7 costimulation has been implicated in the induction and progression of autoimmune diseases. Experimentally induced models of autoimmunity have been shown to be prevented or reduced in intensity in mice rendered deficient for CD28 costimulation. In sharp contrast, spontaneous diabetes is exacerbated in both B7-1/B7-2-deficient and CD28-deficient NOD mice. These mice present a profound decrease of the immunoregulatory CD4+CD25+ T cells, which control diabetes in prediabetic NOD mice. These cells are absent from both CD28KO and B7-1/B7-2KO mice, and the transfer of this regulatory T cell subset from control NOD animals into CD28-deficient animals can delay/prevent diabetes. The results suggest that the CD28/ B7 costimulatory pathway is essential for the development and homeostasis of regulatory T cells that control spontaneous autoimmune diseases.

L12 ANSWER 10 OF 14 MEDLINE on STN
AB Transforming growth factor-beta 1 (TGF-beta 1) is a cytokine with complex immunomodulatory effects including the ability to inhibit the onset or severity of autoimmune disease. This study was designed to test the possibility that one mechanism by which TGF-beta 1 exerts its immunosuppressive effects is by inducing antigen (Ag)-specific unresponsiveness in CD4+ cells. TGF-beta 1 was shown here to inhibit the Ag-specific proliferation of naive CD4+ cells from T cell receptor (TCR) transgenic mice. More importantly, the naive CD4+ cells exposed to TGF-beta 1 and Ag, but not to TGF-beta 1 alone, in primary cultures were unable to proliferate or secrete IL-2 in response to a subsequent Ag challenge following removal of TGF-beta 1 from the cultures. Anti-CD28 mAb partially blocked the Ag-specific inactivation induced by TGF-beta 1 in naive CD4+ cells. The inhibitory effects of TGF-beta 1 on

CD4+ cells are not mediated by alterations in APC costimulation since TGF-beta 1 did not inhibit the Ag-induced expression of MHC class II molecules, CD80 or CD86 on splenic APC. Taken together, the results suggest that the immunosuppressive activities of TGF-beta 1 encompass direct induction of Ag-specific unresponsiveness in naive CD4+ cells.

L12 ANSWER 11 OF 14 MEDLINE on STN

AB BACKGROUND: T lymphocytes require two important signals for efficient activation: 1) recognition of antigens bound to self major histocompatibility complex antigens, and 2) simultaneous stimulation via so-called costimulatory molecules. Interaction of the costimulatory B7 molecules on antigen presenting cells with CD28 on T lymphocytes appears to be particularly important, as it modifies secretion of cytokines, especially interleukin 2. In primary biliary cirrhosis biliary epithelial cells aberrantly express major histocompatibility complex class II antigens and may function as antigen presenting cells. METHODS: We studied expression of HLA-DR, B7-1, B7-2 and CD28 on cryostat liver sections in 16 patients with primary biliary cirrhosis, three patients each with autoimmune hepatitis and primary sclerosing cholangitis and nine patients with chronic viral hepatitis (five hepatitis B, four hepatitis C) using mouse monoclonal antibodies in an indirect immunoperoxidase technique. RESULTS: In advanced primary biliary cirrhosis, HLA-DR was found on 57% of bile ducts, B7-2 on 5% of bile ducts, and B7-1 could not be detected on any bile duct. Neither B7-1 nor B7-2 was seen on bile ducts in the four patients with early primary biliary cirrhosis. HLA-DR+ bile ducts also lacked expression of B7 molecules in autoimmune hepatitis. In contrast, HLA-DR, B7-1 and B7-2 were expressed simultaneously on professional antigen presenting cells such as macrophages in epitheloid granulomas. CONCLUSION: HLA-DR+ biliary epithelial cells in primary biliary cirrhosis insufficiently co-express B7-1 or B7-2 molecules. Therefore, they must either use different costimulatory molecules, or otherwise are deficient in lymphocyte activation. Since recognition of antigen in the absence of B7-CD28 interaction may lead to anergy of lymphocytes, this might contribute to the impaired cytokine secretion found in primary biliary cirrhosis.

L12 ANSWER 12 OF 14 MEDLINE on STN

AB Expression of the co-stimulatory molecule B7-1 (CD80) on pancreatic beta cells can overcome peripheral T cell tolerance in transgenic models of autoimmune disease. This study aimed to determine if aberrant B7-1 or B7-2 (CD86) expression on pancreatic beta cells is involved in the pathogenesis of autoimmune diabetes in non-obese diabetic (NOD) mice. Immunohistochemical analysis of NOD pancreas sections revealed no evidence of B7-1 or B7-2 expression on pancreatic beta cells at any stage prior to the onset of either spontaneously arising or cyclophosphamide-accelerated diabetes. Likewise, the NOD-derived NIT-1 beta cell line did not express surface B7 or B7-1 mRNA either constitutively or following exposure to IFN-gamma and TNF-alpha, two cytokines known to be present in the insulitis lesion of NOD mice, or cAMP which can induce B7-1 expression on B cells. Both B7-1 and B7-2 were, however, highly expressed on the majority of islet-infiltrating inflammatory cells in NOD mice between days 7 and 12 after the administration of cyclophosphamide which results in accelerated beta cell destruction. Likewise B7-1 and B7-2 were extensively expressed on islet-infiltrating cells present at the time of diabetes onset in NOD SCID mice with adoptively transferred diabetes. By immunohistochemistry and flow cytometry, it was determined that the phenotype of B7+ cells in

the pancreas of NOD mice 9 days after cyclophosphamide included a mixture of macrophages and both CD4+ and CD8+ T cells. B7-2 was also expressed on islet-infiltrating cells in the spontaneously occurring diabetes of female NOD mice, but the levels of B7-1 expression were low in comparison with the accelerated models of diabetes. RIP-IL-2 transgenic mice, which have extensive islet infiltration but no autoimmune beta cell destruction, also had virtually no B7-1 expression and a minority of B7-2-expressing inflammatory cells. Thus, the activation of beta cell-specific T cells in NOD mice does not appear to be a result of aberrant expression of B7 on the beta cells. Expression of B7-1 and B7-2 on islet-infiltrating cells is, however, associated with autoimmune beta cell destruction, suggesting a role for the B7-CD28 interaction in this process.

L12 ANSWER 13 OF 14 MEDLINE on STN
AB CTLA-4, a CD28 homologue expressed on activated T cells, binds with high affinity to the CD28 ligands, B7-1 (CD80) and B7-2 (CD86). This study was designed to examine the role of CTLA-4 in regulating autoimmune disease. Murine relapsing-remitting experimental autoimmune encephalomyelitis (R-EAE) is a demyelinating disease mediated by PLP139-151-specific CD4+ T cells in SJL/J mice. Anti-CTLA-4 mAbs (or their F(ab) fragments) enhanced in vitro proliferation and pro-inflammatory cytokine production by PLP139-151-primed lymph node cells. Addition of either reagent to in vitro activation cultures potentiated the ability of T cells to adoptively transfer disease to naive recipients. In vivo administration of anti-CTLA-4 mAb to recipients of PLP139-151-specific T cells resulted in accelerated and exacerbated disease. Finally, anti-CTLA-4 treatment of mice during disease remission resulted in the exacerbation of relapses. Collectively, these results suggest that CTLA-4 mediates the downregulation of ongoing immune responses and plays a major role in regulating autoimmunity.

L12 ANSWER 14 OF 14 MEDLINE on STN
AB The B7 family of cell surface molecules expressed on APC provides accessory signals to T cells via either CD28 or CTLA-4. However, while CD28 transduces a costimulatory signal that is required for an optimal immune response, CTLA-4 transmits a negative signal. These studies use an anti-CTLA-4 mAb to directly address the role of this T cell surface molecule in experimental allergic encephalomyelitis (EAE). CTLA-4 regulation of disease was assessed during initial immune cell interactions and during the effector stage of the encephalitogenic immune response. The effects of anti-CTLA-4 treatment were schedule dependent. CTLA-4 blockade during the onset of clinical symptoms markedly exacerbated disease, enhancing mortality. Disease exacerbation was associated with enhanced production of the encephalitogenic cytokines TNF-alpha, IFN-gamma and IL-2. Hence, CTLA-4 regulates the intensity of the autoimmune response in EAE, attenuating inflammatory cytokine production and clinical disease manifestations.

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The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d all

L12 ANSWER 1 OF 14 MEDLINE on STN

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AN 2004556430 MEDLINE
DN PubMed ID: 15528977
TI Inhibition of lymphocyte activation and function by the prenylation inhibitor L-778,123.
AU Si Ming-Sing; Reitz Bruce A; Borie Dominic C
CS Transplantation Immunology Laboratory, Department of Cardiothoracic Surgery, Falk Cardiovasular Research Center, Stanford University School of Medicine, Stanford, CA 95305-5407, USA.
NC 1F32AI051094 (NIAID)
SO Investigational new drugs, (2005 Jan) Vol. 23, No. 1, pp. 21-9. Journal code: 8309330. ISSN: 0167-6997.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200506
ED Entered STN: 6 Nov 2004
Last Updated on STN: 3 Jun 2005
Entered Medline: 2 Jun 2005
AB Prenylated Ras GTPases transduce signals from the T cell receptor, CD28 costimulatory receptor and IL-2 receptor. Since signals from these receptors mediate T cell activation, proliferation and survival, we hypothesized that the prenylation inhibitor L-778,123 would impart immunomodulation.The effect of L-778,123 on T cell activation (CD71 or CD25 surface expression) was determined by flow cytometry. Peripheral blood mononuclear cell (PBMC) proliferation in the presence of L-778,123 and/or cyclosporine (CsA) was determined by [3H]thymidine incorporation. The ability of L-778,123 to inhibit IL-2 receptor signaling was investigated by measuring IL-2 induced proliferation in CTLL-2 cells and IL-2 prevention of apoptosis in activated human PBMC. L-778,123 inhibited lectin induced expression of CD71 and CD25 with IC50's of 6.48 +/- 1.31 microM and 84.1 +/- 50.0 microM, respectively. PBMC proliferation was inhibited by L-778,123 with an IC50 of 0.92 +/- 0.23 microM, and addition of CsA did not increase the potency. L-778,123 did not inhibit IL-2 and IFN-gamma production by T cells. L-778,123 abrogated IL-2 induced proliferation of CTLL-2 cells with an IC50 of 0.81 +/- 0.44 microM. However, L-778,123 minimally reversed the prosurvival effect of IL-2 in activated lymphocytes. IL-2 ligand and receptor production during T cell activation are relatively unaffected by L-778,123. However, the activation and proliferative effects of IL-2 on T cells are potently blocked by L-778,123. These results reveal a selective blockade of the IL-2 cytokine axis distal to the IL-2 receptor by the L-778,123 and warrant evaluation of prenylation inhibitors in treating transplant rejection and autoimmune diseases.
CT Antigens, CD28: ME, metabolism
Antigens, CD80: ME, metabolism
Apoptosis: DE, drug effects
Cell Proliferation: DE, drug effects
Cyclosporine: PD, pharmacology
Dimethylallyltranstransferase: AI, antagonists & inhibitors
*Enzyme Inhibitors: PD, pharmacology
Flow Cytometry
Humans
*Imidazoles: PD, pharmacology
Interferon Type II: ME, metabolism
Interleukin-2: PD, pharmacology
Ligands
*Lymphocyte Activation: DE, drug effects
*Protein Isoprenylation: DE, drug effects

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50613257

Receptors, Interleukin-2: AI, antagonists & inhibitors
Receptors, Interleukin-2: ME, metabolism
Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Signal Transduction: DE, drug effects
*T-Lymphocytes: DE, drug effects
T-Lymphocytes: IM, immunology
RN 59865-13-3 (Cyclosporine); 82115-62-6 (Interferon Type II)
CN 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Enzyme Inhibitors); 0 (Imidazoles); 0 (Interleukin-2); 0 (L 778,123); 0 (Ligands); 0 (Receptors, Interleukin-2); EC 2.5.1.1 (Dimethylallyltranstransferase)

=> d all 2-14

L12 ANSWER 2 OF 14 MEDLINE on STN
AN 2003464446 MEDLINE
DN PubMed ID: 14500627
TI Cutting edge: CD28 controls peripheral homeostasis of CD4+CD25+ regulatory T cells.
AU Tang Qizhi; Henriksen Kammi J; Boden Elisa K; Tooley Aaron J; Ye Jianqin; Subudhi Sumit K; Zheng Xin X; Strom Terry B; Bluestone Jeffrey A
CS University of California San Francisco Diabetes Center, University of California, San Francisco, CA 94143, USA.
NC AI466430 (NIAID)
F32 AI10360 (NIAID)
SO Journal of immunology (Baltimore, Md. : 1950), (2003 Oct 1) Vol. 171, No. 7, pp. 3348-52.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200401
ED Entered STN: 8 Oct 2003
Last Updated on STN: 8 Jan 2004
Entered Medline: 7 Jan 2004
AB CD28/B7 blockade leads to exacerbated autoimmune disease in the nonobese diabetic mouse strain as a result of a marked reduction in the number of CD4(+)CD25(+) regulatory T cells (Tregs). Herein, we demonstrate that CD28 controls both thymic development and peripheral homeostasis of Tregs. CD28 maintains a stable pool of peripheral Tregs by both supporting their survival and promoting their self-renewal. CD28 engagement promotes survival by regulating IL-2 production by conventional T cells and CD25 expression on Tregs.
CT Animals
Antigens, CD: PD, pharmacology
Antigens, CD: PH, physiology
Antigens, CD28: ME, metabolism
*Antigens, CD28: PH, physiology
Antigens, CD80: PD, pharmacology
Antigens, CD80: PH, physiology
Antigens, CD86
*CD4-Positive T-Lymphocytes: CY, cytology
*CD4-Positive T-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: ME, metabolism

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Cell Differentiation: IM, immunology
Cell Division: IM, immunology
Cell Survival: IM, immunology
*Homeostasis: IM, immunology
Interleukin-2: PH, physiology
Lymph Nodes: CY, cytology
Lymph Nodes: IM, immunology
Lymph Nodes: ME, metabolism
Membrane Glycoproteins: PD, pharmacology
Membrane Glycoproteins: PH, physiology
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Mice, Inbred NOD
Mice, Knockout
Mice, Transgenic
*Receptors, Interleukin-2: BI, biosynthesis
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Spleen: CY, cytology
Spleen: IM, immunology
Spleen: ME, metabolism
*T-Lymphocyte Subsets: CY, cytology
*T-Lymphocyte Subsets: IM, immunology
T-Lymphocyte Subsets: ME, metabolism
Thymus Gland: CY, cytology
Thymus Gland: IM, immunology
Thymus Gland: ME, metabolism

CN 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Cd86 protein, mouse); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Receptors, Interleukin-2)

L12 ANSWER 3 OF 14 MEDLINE on STN
AN 2002148657 MEDLINE
DN PubMed ID: 11857337
TI PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2.
AU Carter LauraL; Fouser Lynette A; Jussif Jason; Fitz Lori; Deng Bija; Wood Clive R; Collins Mary; Honjo Tasuku; Freeman Gordon J; Carreno Beatriz M
CS Wyeth-Genetics Institute, Cambridge, MA 02140, USA.. LCarter@genetics.com
SO European journal of immunology, (2002 Mar) Vol. 32, No. 3, pp. 634-43. Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 8 Mar 2002
Last Updated on STN: 30 Apr 2002
Entered Medline: 29 Apr 2002
AB Programmed death-1 (PD-1) is an immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing receptor expressed upon T cell activation. PD-1(-/-) animals develop autoimmune diseases, suggesting an inhibitory role for PD-1 in immune responses. Members of the B7 family, PD-L1 and PD-L2, are ligands for PD-1. This study examines the functional consequences of PD-1:PD-L engagement on murine CD4 and CD8 T cells and shows that these interactions result in inhibition of proliferation and cytokine production. T cells stimulated with

anti-CD3/PD-L1.Fc-coated beads display dramatically decreased proliferation and IL-2 production, while CSFE analysis shows fewer cells cycling and a slower division rate. Costimulation with soluble anti-CD28 mAb can overcome PD-1-mediated inhibition by augmenting IL-2 production. However, PD-1:PD-L interactions inhibit IL-2 production even in the presence of costimulation and, thus, after prolonged activation, the PD-1:PD-L inhibitory pathway dominates. Exogenous IL-2 is able to overcome PD-L1-mediated inhibition at all times, indicating that cells maintain IL-2 responsiveness. Experiments using TCR transgenic CD4(+) or CD8(+) T cells stimulated with antigen-presenting cells expressing PD-L1 show that both T cell subsets are susceptible to this inhibitory pathway. However, CD8(+) T cells may be more sensitive to modulation by the PD-1:PD-L pathway because of their intrinsic inability to produce significant levels of IL-2.

CT Check Tags: Female
Amino Acid Sequence
Animals
Antibodies, Monoclonal: IM, immunology
Antibodies, Monoclonal: PD, pharmacology
Antigen Presentation
Antigens, CD29: IM, immunology
Antigens, CD3: IM, immunology
*Antigens, CD80
*Antigens, Surface
Apoptosis: DE, drug effects
*Apoptosis: PH, physiology
Apoptosis Regulatory Proteins
*Blood Proteins
CD4-Positive T-Lymphocytes: CY, cytology
CD4-Positive T-Lymphocytes: DE, drug effects
*CD4-Positive T-Lymphocytes: ME, metabolism
CD8-Positive T-Lymphocytes: CY, cytology
CD8-Positive T-Lymphocytes: DE, drug effects
*CD8-Positive T-Lymphocytes: ME, metabolism
CD8-Positive T-Lymphocytes: SE, secretion
Cell Division
Cell Line
Immunoglobulin Fc Fragments: IM, immunology
Interleukin-2: PD, pharmacology
*Interleukin-2: PH, physiology
Kinetics
Ligands
Lymphocyte Activation: DE, drug effects
Membrane Glycoproteins
Mice
Mice, Inbred BALB C
Mice, Transgenic
Microspheres
Molecular Sequence Data
*Peptides: PH, physiology
*Proteins: PH, physiology
Receptors, Antigen, T-Cell: GE, genetics

CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD29); 0 (Antigens, CD3); 0 (Antigens, CD80); 0 (Antigens, Surface); 0 (Apoptosis Regulatory Proteins); 0 (Blood Proteins); 0 (Immunoglobulin Fc Fragments); 0 (Interleukin-2); 0 (Ligands); 0 (Membrane Glycoproteins); 0 (Pdcd1 protein, mouse); 0 (Pdcd1lg1 protein, mouse); 0 (Pdcd1lg2 protein, mouse); 0 (Peptides); 0 (Proteins); 0 (Receptors, Antigen, T-Cell)

Erich Leeser

50613257

L12 ANSWER 4 OF 14 MEDLINE on STN
AN 2002093778 MEDLINE
DN PubMed ID: 11810061
TI Immunomodulation with CTLA4-Ig in islet transplantation.
AU Benhamou Pierre Y
CS Department of Endocrinology, CHU, Grenoble, France.. benhamou@ujf-grenoble.fr
SO Transplantation, (2002 Jan 15) Vol. 73, No. 1 Suppl, pp. S40-2. Ref: 33
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 2 Feb 2002
Last Updated on STN: 14 Feb 2002
Entered Medline: 13 Feb 2002
AB The need for permanent, nonspecific, and potentially harmful immunosuppression remains a major obstacle for islet transplantation. The response of a type 1 diabetic recipient to an islet graft includes a specific allogenic immune response and the recurrence of autoimmunity. Free or encapsulated in an immunoisolation device, islet cells are exposed to immune aggression, initiated by donor antigen-presenting cells or by indirect, host antigen-presenting cell-mediated antigen presentation. CTLA4-Ig is a genetically engineered fusion protein of human CTLA4 and the IgG 1 Fc region. It prevents T-cell activation by binding to human B7, which costimulates T cells through CD28. Interesting data were reported in experimental islet transplantation, suggesting that CTLA4-Ig may be slightly but significantly beneficial to islet allograft survival, although studies in autoimmune diabetes are scarce. The main limitations include transient and low levels of expression when CTLA4-Ig is delivered locally, a predominant effect on the direct recognition pathway, and the lack of effect on memory cells. Clinical trials in islet transplantation could be discussed in nonuremic patients, with steroid-free and anticalcineurin-free regimens, in combination with another costimulation blocker, rapamycin, and an anti-interleukin 2 receptor antibody, and with a strategy directed against the recurrence of autoimmunity.
CT *Adjuvants, Immunologic: PH, physiology
Animals
Antigens, CD28: IM, immunology
Antigens, CD80: IM, immunology
*Antigens, Differentiation: IM, immunology
Autoimmune Diseases: IM, immunology
Diabetes Mellitus: IM, immunology
Humans
*Immunoconjugates
*Islets of Langerhans Transplantation: IM, immunology
CN 0 (Adjuvants, Immunologic); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (Immunoconjugates); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L12 ANSWER 5 OF 14 MEDLINE on STN
AN 2001677041 MEDLINE
DN PubMed ID: 11722623
TI Control of T-cell activation by CD4+ CD25+ suppressor T cells.
AU Shevach E M; McHugh R S; Piccirillo C A; Thornton A M

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50613257

CS Cellular Immunology Section, Laboratory of Immunology, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.. ems1@mail.nih.gov
SO Immunological reviews, (2001 Aug) Vol. 182, pp. 58-67. Ref: 35
Journal code: 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 28 Nov 2001
Last Updated on STN: 9 Feb 2002
Entered Medline: 8 Feb 2002
AB Depletion of the minor (approximately 10%) subpopulation of CD4+ T cells that co-expresses CD25 (interleukin (IL)-2 receptor alpha-chain) by thymectomy of neonates on the third day of life or by treatment of adult CD4+ T cells with anti-CD25 and complement results in the development of organ-specific autoimmunity. Autoimmune disease can be prevented by reconstitution of the animals with CD4+ CD25+ cells. CD4+ CD25+-mediated protection of autoimmune gastritis does not require the suppressor cytokines IL-4, IL-10, or transforming growth factor (TGF)-beta. Mice that express a transgenic T-cell receptor (TCR) derived from a thymectomized newborn that recognizes the gastric parietal cell antigen H/K ATPase all develop severe autoimmune gastritis very early in life. CD4+ CD25+ T cells are also powerful suppressors of the activation of both CD4+ and CD8+ T cells in vitro. Suppression is mediated by a cell contact-dependent, cytokine-independent T-T interaction. Activation of CD4+ CD25+ via their TCR generates suppressor effector cells that are capable of non-specifically suppressing the activation of any CD4+ or CD8+ T cell. Activation of suppressor effector function is independent of co-stimulation mediated by CD28/CTLA-4 interactions with CD80/CD86. We propose that CD4+ CD25+ T cells recognize organ-specific antigens, are recruited to sites of autoimmune damage where they are activated by their target antigen, and then physically interact with autoreactive CD4+ or CD8+ effector cells to suppress the development of autoimmune disease.
CT Animals
Autoimmune Diseases: IM, immunology
CD4-Positive T-Lymphocytes: CY, cytology
*CD4-Positive T-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: ME, metabolism
Cell Division
Humans
*Lymphocyte Activation
Organ Specificity
Receptors, Antigen, T-Cell: IM, immunology
*Receptors, Interleukin-2: IM, immunology
T-Lymphocytes, Regulatory: CY, cytology
*T-Lymphocytes, Regulatory: IM, immunology
T-Lymphocytes, Regulatory: ME, metabolism
Thymus Gland: CY, cytology
Thymus Gland: IM, immunology
Transgenes
CN 0 (Receptors, Antigen, T-Cell); 0 (Receptors, Interleukin-2)

L12 ANSWER 6 OF 14 MEDLINE on STN
AN 2001464712 MEDLINE

Erich Leeser

50613257

DN PubMed ID: 11509584
TI Role of CD47 in the induction of human naive T cell anergy.
AU Avice M N; Rubio M; Sergerie M; Delespesse G; Sarfati M
CS Allergy Research Laboratory, Research Center of Centre Hospitalier Universite de Montreal, Notre Dame Hospital, Quebec, Canada.
SO Journal of immunology (Baltimore, Md. : 1950), (2001 Sep 1) Vol. 167, No. 5, pp. 2459-68.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200112
ED Entered STN: 20 Aug 2001
Last Updated on STN: 22 Jan 2002
Entered Medline: 5 Dec 2001
AB We recently reported that CD47 ligation inhibited IL-2 release by umbilical cord blood mononuclear cells activated in the presence of IL-12, but not IL-4, preventing the induction of IL-12Rbeta(2) expression and the acquisition of Th1, but not the Th2 phenotype. Here we show that in the absence of exogenous cytokine at priming, CD47 ligation of umbilical cord blood mononuclear cells promotes the development of hyporesponsive T cells. Naive cells were treated with CD47 mAb for 3 days, expanded in IL-2 for 9-12 days, and restimulated by CD3 and CD28 coengagement. Effector T cells generated under these conditions were considered to be anergic because they produced a reduced amount of IL-2 at the single-cell level and displayed an impaired capacity 1) to proliferate, 2) to secrete Th1/Th2 cytokines, and 3) to respond to IL-2, IL-4, or IL-12. Moreover, CD47 mAb strongly suppressed IL-2 production and IL-2Ralpha expression in primary cultures and IL-2 response of activated naive T cells. Induction of anergy by CD47 mAb was IL-10 independent, whereas inclusion of IL-2 and IL-4, but not IL-7, at priming fully restored T cell activation. Furthermore, CD28 costimulation prevented induction of anergy. Thus, CD47 may represent a potential target to induce anergy and prevent undesired Th0/Th1 responses such as graft vs host diseases, allograft rejection, or autoimmune diseases.
CT Antibodies, Monoclonal: PD, pharmacology
*Antigens, CD: IM, immunology
Antigens, CD: ME, metabolism
Antigens, CD28: ME, metabolism
Antigens, CD47
Antigens, CD80: ME, metabolism
Antigens, CD86
*Carrier Proteins: IM, immunology
*Clonal Anergy
Clonal Anergy: DE, drug effects
Cytokines: BI, biosynthesis
Fetal Blood: CY, cytology
Fetal Blood: IM, immunology
Humans
In Vitro
Infant, Newborn
Interleukin-10: PD, pharmacology
Interleukin-2: BI, biosynthesis
Interleukin-2: PD, pharmacology
Interleukin-4: PD, pharmacology
Lymphocyte Activation
Membrane Glycoproteins: ME, metabolism

Erich Leeser

50613257

Phenotype
Receptors, Interleukin-2: BI, biosynthesis
Research Support, Non-U.S. Gov't
Signal Transduction
*T-Lymphocytes: IM, immunology
RN 130068-27-8 (Interleukin-10); 207137-56-2 (Interleukin-4)
CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD47); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (CD47 protein, human); 0 (CD86 protein, human); 0 (Carrier Proteins); 0 (Cytokines); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Receptors, Interleukin-2)

L12 ANSWER 7 OF 14 MEDLINE on STN
AN 2001417208 MEDLINE
DN PubMed ID: 11466340
TI CD4+CD25high regulatory cells in human peripheral blood.
AU Baecher-Allan C; Brown J A; Freeman G J; Hafler D A
CS Laboratory of Molecular Immunology, Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA 02115.. callan@rics.bwh.harvard.edu
NC AI39671 (NIAID)
AI41584 (NIAID)
CA84500 (NCI)
P01 AI39671 (NIAID)
P01 NS38037 (NINDS)
R01 ND24247-10
SO Journal of immunology (Baltimore, Md. : 1950), (2001 Aug 1) Vol. 167, No. 3, pp. 1245-53.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200110
ED Entered STN: 29 Oct 2001
Last Updated on STN: 29 Oct 2001
Entered Medline: 25 Oct 2001
AB Thymectomy in mice on neonatal day 3 leads to the development of multiorgan autoimmune disease due to loss of a CD(+)CD25(+) T cell regulatory population in their peripheral lymphoid tissues. Here, we report the identification of a CD4(+) population of regulatory T cells in the circulation of humans expressing high levels of CD25 that exhibit in vitro characteristics identical with those of the CD4(+)CD25(+) regulatory cells isolated in mice. With TCR cross-linking, CD4(+)CD25(high) cells did not proliferate but instead totally inhibited proliferation and cytokine secretion by activated CD4(+)CD25(-) responder T cells in a contact-dependent manner. The CD4(+)CD25(high) regulatory T cells expressed high levels of CD45RO but not CD45RA, akin to the expression of CD45RB(low) on murine CD4(+)CD25(+) regulatory cells. Increasing the strength of signal by providing either costimulation with CD28 cross-linking or the addition of IL-2 to a maximal anti-CD3 stimulus resulted in a modest induction of proliferation and the loss of observable suppression in cocultures of CD4(+)CD25(high) regulatory cells and CD4(+)CD25(-) responder cells. Whereas higher ratios of CD4(+)CD25(high) T cells are required to suppress proliferation if the PD-L1 receptor is blocked, regulatory cell function is shown to persist in the absence of the PD-1/PD-L1 or CTLA-4/B7 pathway. Thus, regulatory CD4 T cells expressing high levels of the IL-2 receptor are present in humans, providing the opportunity to determine whether alterations of these

Erich Leeser

50613257

populations of T cells are involved in the induction of human autoimmune disorders.

CT *Antigens, CD4: BI, biosynthesis
Antigens, CD4: BL, blood
Antigens, CD45: BI, biosynthesis
*Antigens, CD80
Antigens, Differentiation: PH, physiology
*Blood Proteins
*CD4-Positive T-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: ME, metabolism
Cells, Cultured
Coculture Techniques
HLA-DR Antigens: BI, biosynthesis
Humans
*Immunoconjugates
Immunosuppressive Agents: PD, pharmacology
Interleukin-2: AI, antagonists & inhibitors
Interleukin-2: GE, genetics
Kinetics
Lymphocyte Activation
Lymphocyte Count
Membrane Glycoproteins
Peptides: PH, physiology
RNA, Messenger: AI, antagonists & inhibitors
RNA, Messenger: ME, metabolism
Receptors, Antigen, T-Cell: IM, immunology
Receptors, Antigen, T-Cell: ME, metabolism
Receptors, Antigen, T-Cell: PH, physiology
*Receptors, Interleukin-2: BI, biosynthesis
Receptors, Interleukin-2: BL, blood
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Signal Transduction: IM, immunology
*T-Lymphocyte Subsets: IM, immunology
T-Lymphocyte Subsets: ME, metabolism

CN 0 (Antigens, CD4); 0 (Antigens, CD45); 0 (Antigens, CD80); 0 (Antigens, Differentiation); 0 (Blood Proteins); 0 (CD274 protein, human); 0 (HLA-DR Antigens); 0 (Immunoconjugates); 0 (Immunosuppressive Agents); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Peptides); 0 (RNA, Messenger); 0 (Receptors, Antigen, T-Cell); 0 (Receptors, Interleukin-2); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L12 ANSWER 8 OF 14 MEDLINE on STN
AN 2001033134 MEDLINE
DN PubMed ID: 11046033
TI Blockade of costimulation through B7/CD28 inhibits experimental autoimmune uveoretinitis, but does not induce long-term tolerance.
AU Silver P B; Hathcock K S; Chan C C; Wiggert B; Caspi R R
CS Laboratory of Immunology and Laboratory of Retinal Cell and Molecular Biology, National Eye Institute, and Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SO Journal of immunology (Baltimore, Md. : 1950), (2000 Nov 1) Vol. 165, No. 9, pp. 5041-7.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

Erich Leeser

50613257

FS Abridged Index Medicus Journals; Priority Journals
EM 200011
ED Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 30 Nov 2000

AB It has been reported that costimulation blockade can result in T cell anergy. We investigated the effects of blocking costimulatory molecules in vivo on the development of experimental autoimmune uveoretinitis (EAU), a model for autoimmune uveitis in humans that is induced in mice by immunization with the retinal Ag interphotoreceptor retinoid binding protein. B10.A mice immunized with a uveitogenic regimen of interphotoreceptor retinoid-binding protein were treated with Abs to B7.1 and B7.2 for 2 wk. Evaluation of EAU and immunological responses 1 wk later showed that disease had been abrogated, and cellular responses were suppressed. To determine whether the costimulation blockade resulted in tolerance, adult-thymectomized mice immunized for uveitis and treated with anti-B7 or anti-CD28 were rechallenged for uveitis induction 5 wk after the initial immunization. Although confirmed to be disease free after the initial immunization, both anti-B7- and anti-CD28 -treated mice developed severe EAU and elevated cellular responses after the rechallenge, equivalent to those of control mice. We conclude that in this model costimulatory blockade in vivo prevents the development of autoimmune disease, but does not result in long-term tolerance. The data are compatible with the interpretation that B7/CD28 blockade prevents generation of effector, but not of memory, T cells.

CT Animals
Antibodies, Blocking: AD, administration & dosage
Antibodies, Monoclonal: AD, administration & dosage
*Antigens, CD: IM, immunology
Antigens, CD: PH, physiology
*Antigens, CD28: IM, immunology
Antigens, CD28: PH, physiology
*Antigens, CD80: IM, immunology
Antigens, CD80: PH, physiology
Antigens, CD86
Cells, Cultured
Eye Proteins: AD, administration & dosage
Eye Proteins: AI, antagonists & inhibitors
Eye Proteins: IM, immunology
*Immune Tolerance: IM, immunology
Immunosuppressive Agents: AD, administration & dosage
Injections, Intraperitoneal
Injections, Subcutaneous
Interferon Type II: BI, biosynthesis
Interleukin-2: AI, antagonists & inhibitors
Interleukin-2: BI, biosynthesis
Interleukin-2: PD, pharmacology
Lymphocyte Activation: IM, immunology
*Membrane Glycoproteins: IM, immunology
Membrane Glycoproteins: PH, physiology
Mice
Mice, Inbred A
Mice, Inbred C57BL
*Retinitis: IM, immunology
*Retinitis: PC, prevention & control
Retinol-Binding Proteins: AD, administration & dosage
Retinol-Binding Proteins: AI, antagonists & inhibitors
Retinol-Binding Proteins: IM, immunology

Erich Leeser

50613257

Th2 Cells: IM, immunology
Th2 Cells: ME, metabolism
*Uveitis: IM, immunology
*Uveitis: PC, prevention & control
RN 82115-62-6 (Interferon Type II)
CN 0 (Antibodies, Blocking); 0 (Antibodies, Monoclonal); 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Cd86 protein, mouse); 0 (Eye Proteins); 0 (Immunosuppressive Agents); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Retinol-Binding Proteins); 0 (retinol-binding glycoprotein)

L12 ANSWER 9 OF 14 MEDLINE on STN
AN 2000254758 MEDLINE
DN PubMed ID: 10795741
TI B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes.
AU Salomon B; Lenschow D J; Rhee L; Ashourian N; Singh B; Sharpe A; Bluestone J A
CS Committee on Immunology, Ben May Institute for Cancer Research and Department of Pathology, University of Chicago, Illinois 60637, USA.
NC DK49799 (NIDDK)
SO Immunity, (2000 Apr) Vol. 12, No. 4, pp. 431-40.
Journal code: 9432918. ISSN: 1074-7613.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 6 Jun 2000
Last Updated on STN: 6 Jun 2000
Entered Medline: 23 May 2000
AB CD28/B7 costimulation has been implicated in the induction and progression of autoimmune diseases. Experimentally induced models of autoimmunity have been shown to be prevented or reduced in intensity in mice rendered deficient for CD28 costimulation. In sharp contrast, spontaneous diabetes is exacerbated in both B7-1/B7-2-deficient and CD28-deficient NOD mice. These mice present a profound decrease of the immunoregulatory CD4+CD25+ T cells, which control diabetes in prediabetic NOD mice. These cells are absent from both CD28KO and B7-1/B7-2KO mice, and the transfer of this regulatory T cell subset from control NOD animals into CD28-deficient animals can delay/prevent diabetes. The results suggest that the CD28/ B7 costimulatory pathway is essential for the development and homeostasis of regulatory T cells that control spontaneous autoimmune diseases.
CT Check Tags: Female; Male
Animals
Antigens, CD: GE, genetics
Antigens, CD: IM, immunology
*Antigens, CD28: IM, immunology
Antigens, CD80: GE, genetics
*Antigens, CD80: IM, immunology
Antigens, CD86
Antigens, Differentiation: IM, immunology
Antigens, Differentiation: PD, pharmacology
*Autoimmune Diseases: IM, immunology
*CD4-Positive T-Lymphocytes: IM, immunology
*Diabetes Mellitus, Type 1: IM, immunology

Erich Leeser

50613257

Homeostasis
*Immunoconjugates
*Lymphocyte Activation: IM, immunology
Lymphokines: DF, deficiency
Membrane Glycoproteins: GE, genetics
Membrane Glycoproteins: IM, immunology
Mice
Mice, Inbred NOD
Mice, Knockout
Prediabetic State: IM, immunology
*Receptors, Interleukin-2: AN, analysis
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.

CN 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Antigens, Differentiation); 0 (Cd86 protein, mouse); 0 (Immunoconjugates); 0 (Lymphokines); 0 (Membrane Glycoproteins); 0 (Receptors, Interleukin-2); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L12 ANSWER 10 OF 14 MEDLINE on STN
AN 97389384 MEDLINE
DN PubMed ID: 9246566
TI Transforming growth factor-beta 1 induces antigen-specific unresponsiveness in naive T cells.
AU Gilbert K M; Thoman M; Bauche K; Pham T; Weigle W O
CS University of Arkansas for Medical Sciences, Little Rock 72205, USA.
NC A111576 (NIA)
AG09948 (NIA)
AG12908
SO Immunological investigations, (1997 Jun) Vol. 26, No. 4, pp. 459-72.
Journal code: 8504629. ISSN: 0882-0139.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 13 Oct 1997
Last Updated on STN: 13 Oct 1997
Entered Medline: 29 Sep 1997
AB Transforming growth factor-beta 1 (TGF-beta 1) is a cytokine with complex immunomodulatory effects including the ability to inhibit the onset or severity of autoimmune disease. This study was designed to test the possibility that one mechanism by which TGF-beta 1 exerts its immunosuppressive effects is by inducing antigen (Ag)-specific unresponsiveness in CD4+ cells. TGF-beta 1 was shown here to inhibit the Ag-specific proliferation of naive CD4+ cells from T cell receptor (TCR) transgenic mice. More importantly, the naive CD4+ cells exposed to TGF-beta 1 and Ag, but not to TGF-beta 1 alone, in primary cultures were unable to proliferate or secrete IL-2 in response to a subsequent Ag challenge following removal of TGF-beta 1 from the cultures. Anti-CD28 mAb partially blocked the Ag-specific inactivation induced by TGF-beta 1 in naive CD4+ cells. The inhibitory effects of TGF-beta 1 on CD4+ cells are not mediated by alterations in APC costimulation since TGF-beta 1 did not inhibit the Ag-induced expression of MHC class II molecules, CD80 or CD86 on splenic APC. Taken together, the results suggest that the immunosuppressive activities of TGF-beta 1 encompass direct induction of Ag-specific unresponsiveness in naive CD4+ cells.
CT Check Tags: Male

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50613257

Animals
Antigens
Antigens, CD: ME, metabolism
Antigens, CD80: ME, metabolism
Antigens, CD86
*CD4-Positive T-Lymphocytes: DE, drug effects
*CD4-Positive T-Lymphocytes: IM, immunology
Cells, Cultured
Histocompatibility Antigens Class II: ME, metabolism
Immune Tolerance
Immunosuppressive Agents: PD, pharmacology
Interleukin-2: SE, secretion
Lymphocyte Activation
Membrane Glycoproteins: ME, metabolism
Mice
Mice, Inbred A
Mice, Transgenic
Receptors, Antigen, T-Cell: GE, genetics
Receptors, Antigen, T-Cell: ME, metabolism
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
*Transforming Growth Factor beta: PD, pharmacology
Transforming Growth Factor beta: PH, physiology

CN 0 (Antigens); 0 (Antigens, CD); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Cd86 protein, mouse); 0 (Histocompatibility Antigens Class II); 0 (Immunosuppressive Agents); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Receptors, Antigen, T-Cell); 0 (Transforming Growth Factor beta)

L12 ANSWER 11 OF 14 MEDLINE on STN
AN 97206022 MEDLINE
DN PubMed ID: 9148019
TI Anomalous expression of costimulatory molecules B7-1, B7-2 and CD28 in primary biliary cirrhosis.
AU Spengler U; Leifeld L; Braunschweiger I; Dumoulin F L; Lechmann M; Sauerbruch T
CS Department of General Medicine, University of Bonn, Germany.
SO Journal of hepatology, (1997 Jan) Vol. 26, No. 1, pp. 31-6.
Journal code: 8503886. ISSN: 0168-8278.
CY Denmark
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 23 May 1997
Last Updated on STN: 23 May 1997
Entered Medline: 9 May 1997
AB BACKGROUND: T lymphocytes require two important signals for efficient activation: 1) recognition of antigens bound to self major histocompatibility complex antigens, and 2) simultaneous stimulation via so-called costimulatory molecules. Interaction of the costimulatory B7 molecules on antigen presenting cells with CD28 on T lymphocytes appears to be particularly important, as it modifies secretion of cytokines, especially interleukin 2. In primary biliary cirrhosis biliary epithelial cells aberrantly express major histocompatibility complex class II antigens and may function as antigen

Erich Leeser

presenting cells. METHODS: We studied expression of HLA-DR, B7-1, B7-2 and CD28 on cryostat liver sections in 16 patients with primary biliary cirrhosis, three patients each with autoimmune hepatitis and primary sclerosing cholangitis and nine patients with chronic viral hepatitis (five hepatitis B, four hepatitis C) using mouse monoclonal antibodies in an indirect immunoperoxidase technique. RESULTS: In advanced primary biliary cirrhosis, HLA-DR was found on 57% of bile ducts, B7-2 on 5% of bile ducts, and B7-1 could not be detected on any bile duct. Neither B7-1 nor B7-2 was seen on bile ducts in the four patients with early primary biliary cirrhosis. HLA-DR+ bile ducts also lacked expression of B7 molecules in autoimmune hepatitis. In contrast, HLA-DR, B7-1 and B7-2 were expressed simultaneously on professional antigen presenting cells such as macrophages in epitheloid granulomas. CONCLUSION: HLA-DR+ biliary epithelial cells in primary biliary cirrhosis insufficiently co-express B7-1 or B7-2 molecules. Therefore, they must either use different costimulatory molecules, or otherwise are deficient in lymphocyte activation. Since recognition of antigen in the absence of B7-CD28 interaction may lead to anergy of lymphocytes, this might contribute to the impaired cytokine secretion found in primary biliary cirrhosis.

CT *Antigens, CD: BL, blood
*Antigens, CD28: BL, blood
*Antigens, CD80: BL, blood
Antigens, CD86
*Autoimmune Diseases: IM, immunology
Bile Ducts: IM, immunology
Chronic Disease
HLA-DR Antigens: BL, blood
Hepatitis, Viral, Human: IM, immunology
Humans
Liver: IM, immunology
*Liver Cirrhosis, Biliary: IM, immunology
*Liver Diseases: IM, immunology
Lymphocyte Activation
*Membrane Glycoproteins: BL, blood

CN 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (CD86 protein, human); 0 (HLA-DR Antigens); 0 (Membrane Glycoproteins)

L12 ANSWER 12 OF 14 MEDLINE on STN
AN 96360150 MEDLINE
DN PubMed ID: 8746558
TI Pancreatic expression of B7 co-stimulatory molecules in the non-obese diabetic mouse.
AU Stephens L A; Kay T W
CS Burnet Clinical Research Unit, Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Victoria, Australia.
SO International immunology, (1995 Dec) Vol. 7, No. 12, pp. 1885-95.
Journal code: 8916182. ISSN: 0953-8178.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 6 Nov 1996
Last Updated on STN: 6 Nov 1996
Entered Medline: 23 Oct 1996
AB Expression of the co-stimulatory molecule B7-1 (CD80) on pancreatic beta cells can overcome peripheral T cell tolerance in

transgenic models of autoimmune disease. This study aimed to determine if aberrant B7-1 or B7-2 (CD86) expression on pancreatic beta cells is involved in the pathogenesis of autoimmune diabetes in non-obese diabetic (NOD) mice. Immunohistochemical analysis of NOD pancreas sections revealed no evidence of B7-1 or B7-2 expression on pancreatic beta cells at any stage prior to the onset of either spontaneously arising or cyclophosphamide-accelerated diabetes. Likewise, the NOD-derived NIT-1 beta cell line did not express surface B7 or B7-1 mRNA either constitutively or following exposure to IFN-gamma and TNF-alpha, two cytokines known to be present in the insulitis lesion of NOD mice, or cAMP which can induce B7-1 expression on B cells. Both B7-1 and B7-2 were, however, highly expressed on the majority of islet-infiltrating inflammatory cells in NOD mice between days 7 and 12 after the administration of cyclophosphamide which results in accelerated beta cell destruction. Likewise B7-1 and B7-2 were extensively expressed on islet-infiltrating cells present at the time of diabetes onset in NOD SCID mice with adoptively transferred diabetes. By immunohistochemistry and flow cytometry, it was determined that the phenotype of B7+ cells in the pancreas of NOD mice 9 days after cyclophosphamide included a mixture of macrophages and both CD4+ and CD8+ T cells. B7-2 was also expressed on islet-infiltrating cells in the spontaneously occurring diabetes of female NOD mice, but the levels of B7-1 expression were low in comparison with the accelerated models of diabetes. RIP-IL-2 transgenic mice, which have extensive islet infiltration but no autoimmune beta cell destruction, also had virtually no B7-1 expression and a minority of B7-2-expressing inflammatory cells. Thus, the activation of beta cell-specific T cells in NOD mice does not appear to be a result of aberrant expression of B7 on the beta cells. Expression of B7-1 and B7-2 on islet-infiltrating cells is, however, associated with autoimmune beta cell destruction, suggesting a role for the B7-CD28 interaction in this process.

CT Check Tags: Female; Male
Animals
Antigens, CD: GE, genetics
Antigens, CD: ME, metabolism
Antigens, CD80: GE, genetics
*Antigens, CD80: ME, metabolism
Antigens, CD86
Base Sequence
Cell Line
DNA Primers: GE, genetics
Diabetes Mellitus, Type 1: ET, etiology
Diabetes Mellitus, Type 1: GE, genetics
*Diabetes Mellitus, Type 1: IM, immunology
Flow Cytometry
Gene Expression
Immunohistochemistry
Interleukin-2: GE, genetics
*Islets of Langerhans: IM, immunology
Membrane Glycoproteins: GE, genetics
Membrane Glycoproteins: ME, metabolism
Mice
Mice, Inbred NOD
Mice, SCID
Mice, Transgenic
Molecular Sequence Data
Phenotype
Research Support, Non-U.S. Gov't

CN 0 (Antigens, CD); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Cd86 protein, mouse); 0 (DNA Primers); 0 (Interleukin-2

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); 0 (Membrane Glycoproteins)

L12 ANSWER 13 OF 14 MEDLINE on STN
AN 96343891 MEDLINE
DN PubMed ID: 8760834
TI CTLA-4: a negative regulator of autoimmune disease.
AU Karandikar N J; Vanderlugt C L; Walunas T L; Miller S D; Bluestone J A
CS Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60611, USA.
NC AI35294 (NIAID)
NS26543 (NINDS)
NS30871 (NINDS)
+
SO The Journal of experimental medicine, (1996 Aug 1) Vol. 184, No. 2, pp. 783-8.
Journal code: 2985109R. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 8 Oct 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Sep 1996
AB CTLA-4, a CD28 homologue expressed on activated T cells, binds with high affinity to the CD28 ligands, B7-1 (CD80) and B7-2 (CD86). This study was designed to examine the role of CTLA-4 in regulating autoimmune disease. Murine relapsing-remitting experimental autoimmune encephalomyelitis (R-EAE) is a demyelinating disease mediated by PLP139-151-specific CD4+ T cells in SJL/J mice. Anti-CTLA-4 mAbs (or their F(ab) fragments) enhanced in vitro proliferation and pro-inflammatory cytokine production by PLP139-151-primed lymph node cells. Addition of either reagent to in vitro activation cultures potentiated the ability of T cells to adoptively transfer disease to naive recipients. In vivo administration of anti-CTLA-4 mAb to recipients of PLP139-151-specific T cells resulted in accelerated and exacerbated disease. Finally, anti-CTLA-4 treatment of mice during disease remission resulted in the exacerbation of relapses. Collectively, these results suggest that CTLA-4 mediates the downregulation of ongoing immune responses and plays a major role in regulating autoimmunity.
CT Check Tags: Female
Amino Acid Sequence
Animals
*Antigens, Differentiation: PH, physiology
Autoantigens: IM, immunology
*Encephalomyelitis, Autoimmune, Experimental: IM, immunology
Immunization, Passive
*Immunoconjugates
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
Lymphocyte Activation
Mice
Mice, Inbred Strains
Molecular Sequence Data
Myelin Basic Proteins: CH, chemistry
Myelin Basic Proteins: IM, immunology
Peptides: CH, chemistry
Peptides: IM, immunology

Erich Leeser

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Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
RN 82115-62-6 (Interferon Type II)
CN 0 (Antigens, Differentiation); 0 (Autoantigens); 0 (Immunoconjugates); 0 (Interleukin-2); 0 (Myelin Basic Proteins); 0 (Peptides); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

L12 ANSWER 14 OF 14 MEDLINE on STN
AN 96322716 MEDLINE
DN PubMed ID: 8759711
TI CTLA-4 blockade enhances clinical disease and cytokine production during experimental allergic encephalomyelitis.
AU Perrin P J; Maldonado J H; Davis T A; June C H; Racke M K
CS Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD 20889-5607, USA.. rinOpjp@bumed30.med.navy.mil
SO Journal of immunology (Baltimore, Md. : 1950), (1996 Aug 15) Vol. 157, No. 4, pp. 1333-6.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199609
ED Entered STN: 24 Sep 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 17 Sep 1996
AB The B7 family of cell surface molecules expressed on APC provides accessory signals to T cells via either CD28 or CTLA-4. However, while CD28 transduces a costimulatory signal that is required for an optimal immune response, CTLA-4 transmits a negative signal. These studies use an anti-CTLA-4 mAb to directly address the role of this T cell surface molecule in experimental allergic encephalomyelitis (EAE). CTLA-4 regulation of disease was assessed during initial immune cell interactions and during the effector stage of the encephalitogenic immune response. The effects of anti-CTLA-4 treatment were schedule dependent. CTLA-4 blockade during the onset of clinical symptoms markedly exacerbated disease, enhancing mortality. Disease exacerbation was associated with enhanced production of the encephalitogenic cytokines TNF-alpha, IFN-gamma and IL-2. Hence, CTLA-4 regulates the intensity of the autoimmune response in EAE, attenuating inflammatory cytokine production and clinical disease manifestations.
CT Check Tags: Female
Animals
*Antibodies, Monoclonal: PD, pharmacology
Antigens, CD: PH, physiology
*Antigens, CD28: PH, physiology
Antigens, CD80: PH, physiology
Antigens, CD86
*Antigens, Differentiation: PH, physiology
*Autoimmune Diseases: IM, immunology
*Cytokines: BI, biosynthesis
*Encephalomyelitis, Autoimmune, Experimental: IM, immunology
Humans
*Immunoconjugates
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
Membrane Glycoproteins: PH, physiology
Mice
Rats

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Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Signal Transduction: DE, drug effects
*T-Lymphocytes, Cytotoxic: IM, immunology
Tumor Necrosis Factor-alpha: BI, biosynthesis
RN 82115-62-6 (Interferon Type II)
CN 0 (Antibodies, Monoclonal); 0 (Antigens, CD); 0 (Antigens, CD28); 0 (Antigens, CD80); 0 (Antigens, CD86); 0 (Antigens, Differentiation); 0 (CD86 protein, human); 0 (Cd86 protein, mouse); 0 (Cd86 protein, rat); 0 (Cytokines); 0 (Immunoconjugates); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (Tumor Necrosis Factor-alpha); 0 (abatacept); 0 (cytotoxic T-lymphocyte antigen 4)

Erich Leeser